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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002950136 for a patent by LA TROBE UNIVERSITY as filed on 11 July 2002.

WITNESS my hand this
Twenty-second day of July 2003

J. Billingsley

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TEAM LEADER EXAMINATION
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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Applicant(s):

LA TROBE UNIVERSITY

Invention Title:

N-METHYL AMINO ACIDS

The invention is described in the following statement:

N-METHYL AMINO ACIDS

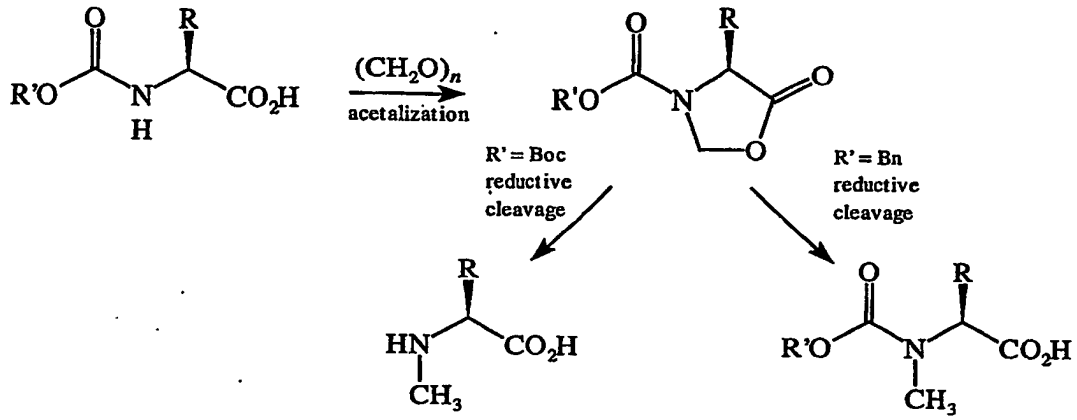
The present invention relates to new N-methyl amino acids and their precursor oxazolidinones, processes for their preparation and their use in the synthesis of peptides. The invention also includes the use of the new N-methyl amino acids together with known N-methyl amino acids in a kit for synthesising peptides.

BACKGROUND OF THE INVENTION

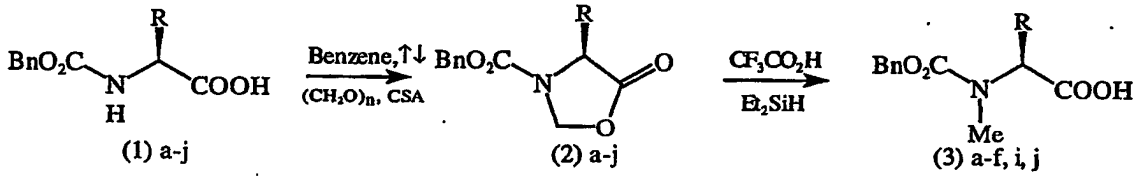
N-methyl amino acids are secondary metabolites present in a wide variety of naturally occurring peptides that display a remarkable range of biological activities including antibiotic, antiviral, anticancer and antifungal. They are also useful compounds for increasing certain pharmacokinetic parameters such as membrane permeability, proteolytic stability and conformational rigidity. In view of the limited availability of N-methyl amino acids, there is a need to prepare such compounds and their precursors for use in the solution and solid phase synthesis of target peptides.

A range of methods have been employed to prepare *N*-methyl amino acids. These include methods for direct methylation, [1-5] reductive amination, [6-12] alternative methods [13-18] and through the generation of oxazolidinones and their subsequent transformation to the *N*-methyl product. [19-23] In addition, there are strategies involving the use of immonium ions in Diels-Alder/retro-Diels-Alder sequences,[24] the nucleophilic displacement of triflates,[25] the hydroxyamination of chiral enolates[26] and the Mitsunobu reaction.[27] Some of these methods suffer from limitations in the range of amino acids to which they are applicable, some utilize rather long synthetic sequences and some cause at least partial racemisation of the substrate. We have exploited oxazolidinone chemistry to generate a range of *N*-methyl amino acids and their precursor oxazolidinones.

The general oxazolidinone route is shown below, where protected amino acids are cyclized efficiently to oxazolidinones. These oxazolidinones may be reductively cleaved by complementary procedures that give *N*-methyl amino acids.

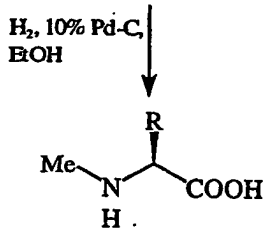


We previously reported[27] the synthesis, *via* the carbamates (1) and the 5-oxazolidinones (2), of a number of new *N*-methyl α-amino acids mainly in the form of their benzyl carbamates (3) and free amino acids (4) as shown below.



(1) a-j (2) a-j (3) a-f, i, j

a R = CH_2OH
b R = $CH(OH)CH_3$
c R = CH_2PhOH
d R = CH_2CH_2COOH (DL)
e R = Ph
f R = $CH_2CH_2CH_2CH_2NPhth$
g R = CH_2SH
h R = $CH_2CH_2SCH_3$
i R = CH_2COOBn
j R = $CH_2CH_2CONHCbz$
k R = $CH_2CH_2CONH_2$
l R = CH_2COOH



(4) a-f*, k, l

*(4f) isolated as *p*-TsOH salt

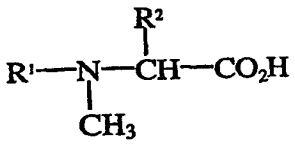
A focus of that study was the endeavour to demonstrate the general applicability of 5-oxazolidinones to the generation of *N*-methyl derivatives of the 20 common natural α-amino acids in the absence of (eg glutamic acid

and tyrosine) or the minimal presence (eg glutamine and aspartic acid) of side chain protecting groups. This approach was designed to emphasise the efficiency of the oxazolidinone route, its mildness, as measured by the lack of racemisation of the α-center, and its chemoselectivity. Indeed, the selectivity of the oxazolidination reaction for the α-amino acid backbone aza and carboxylic functionalities often allowed the subsequent manipulation of reactive sidechains.

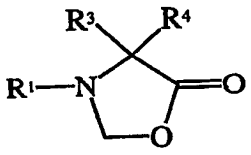
However in the previous paper there were notable failures in the strategy particularly in regard to certain difficult α-amino acids, those bearing sidechains such as histidine and tryptophan. We have now successfully synthesised these outstanding *N*-methyl targets, together with others such as threonine, serine, cysteine, methionine, asparagine, aspartic acid and glutamic acid and their oxazolidinone precursors. As a result, the 5-oxazolidinone route to *N*-methyl amino acids has now been applied to the synthesis of all 20 of the common L-α-amino acids and some related compounds.

SUMMARY OF THE INVENTION

According to the present invention there is provided a compound of formula I or II:



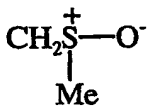
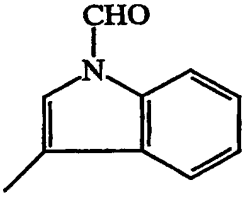
I

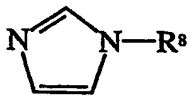
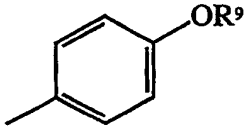
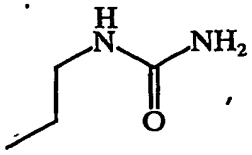
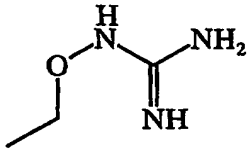


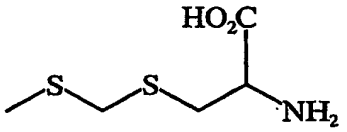
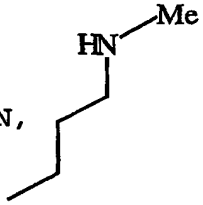
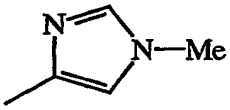
II

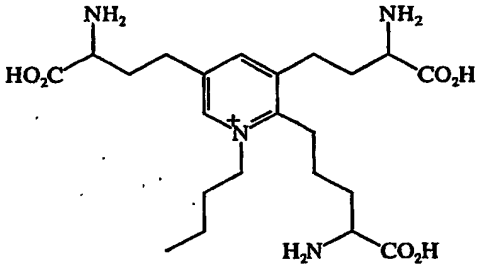
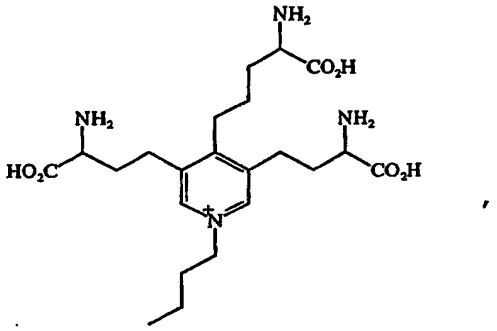
in which

R^1 is an N-protecting group or a peptide;

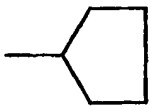
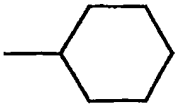
R^2 is $CHCH_3OAc$ or CHR^5R^6 in which R^5 is hydrogen and R^6 is OAc, $CONH_2$, SBn,  ,  ,

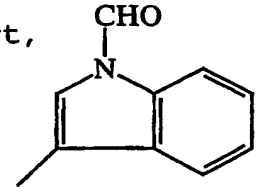
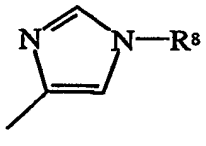
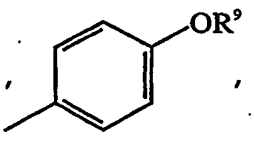
 ,  ,  ,  ,

 , CN,  ,  ,

 ,  ,

CO_2R^7 or $CH_2CO_2R^7$ in which R^7 is is a carboxyl protecting group; and

R^3 is $CHCH_3OAc$,  , 

or CHR^5R^6 in which R^5 is as defined above and R^6 is OAc, SBn, CONHTrt,  ,  ,  ,

CO_2R^7, $CHCO_2R^7$, CH_2CH_3 or $CH{=}CH_2$ in which R^7 is as defined above, R^8 is a histidine protecting group and R^9 is a phenol protecting group;

R^4 is hydrogen or R^4 is methyl when R^3 is OAc; or

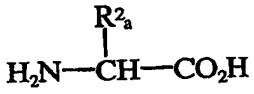
R^3 together with R^4 forms cyclopentyl,

salts, hydrates, solvates, derivatives, tautomers and/or isomers thereof.

The present invention also provides a process for preparing a compound of formula I as defined above which comprises reductive cleavage of a compound of formula II defined above.

The present invention further provides a process for preparing a compound of formula I or II which comprises the steps of:

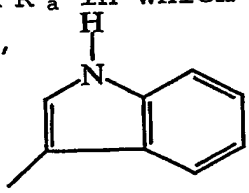
(a) converting a compound of formula III



III

in which

R^2_a is CHOHMe or $CHR^5R^6_a$ in which R^5 is as defined above and R^6_a is OH, SH, $CONH_2$,



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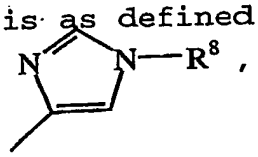
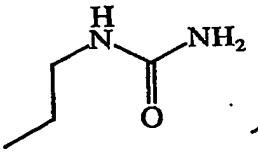


,

in which R^8 is as defined above,



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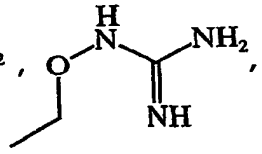

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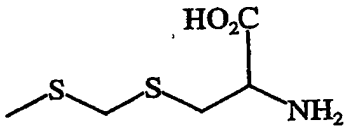

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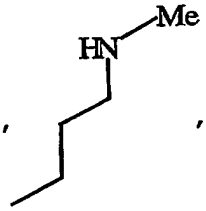

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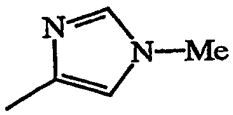

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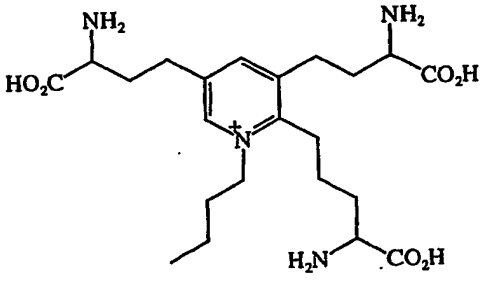

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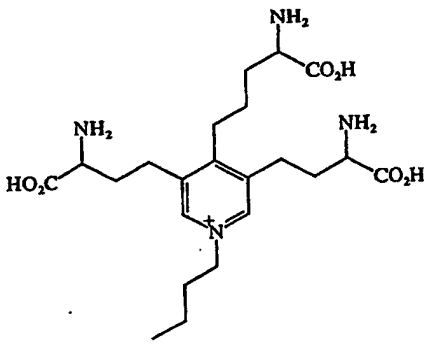
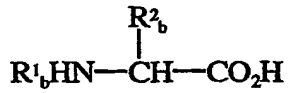


,

CO_2H or CH_2CONH_2

or salts thereof

into a compound of formula IV

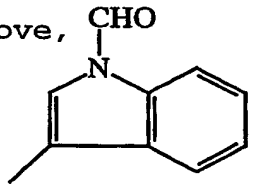
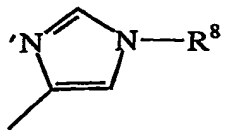
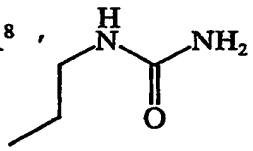
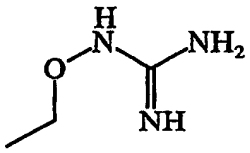
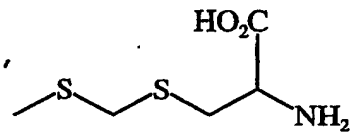
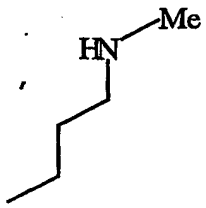
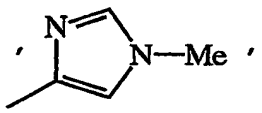
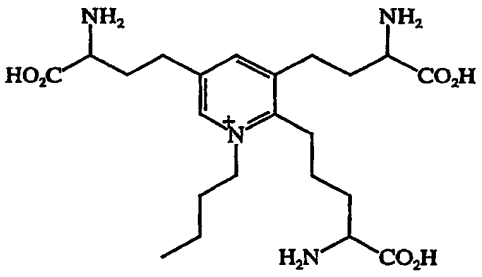
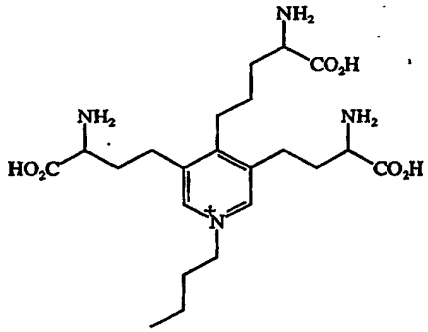


IV

in which

R^1_b is an N-protecting group;

R^2_b is CHOAcMe or $CHR^5R^6_b$ in which R^5 is as defined above and R^6_b is OAc, SBn, SMe, $CONHR^1_b$ in which R^1_b is as defined above,

CO_2H or CH_2CO_2H;

(b) oxazolidination of the compound of formula IV to form the compound of formula II as defined above; and

(c) reductive cleavage of the compound of formula II as defined above to form the compound of formula I as defined above.

Further according to the present invention there is provided use of the compound of formula I or II defined

above in the synthesis of peptides.

Still further according to the present invention there is provided a peptide which includes a compound of formula I or II as defined above.

The invention also extends to a kit for use in synthesising peptides which comprises

(a) at least one compound of formula I or formula II; and

(b) optionally at least one other N-methyl amino acid, its precursor oxazolidinone or protected forms thereof,

said compounds, amino acids and oxazolidinones being held separately.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

The term "N-protecting group" is used herein in its broadest sense and refers to any group capable of protecting the amino group of an amino acid such as those disclosed in Greene, T.W., "*Protective Groups in Organic Synthesis*" John Wiley & Sons, New York 1991, pp 315-398 and 379-385, the contents of which are incorporated herein by reference.

Preferably the N-protecting group is a carbamate such as, 9-fluorenylmethyl carbamate (Fmoc), 2,2,2-trichloroethyl carbamate (Troc), t-butyl carbamate (BOC), allyl carbamate (Alloc), 2-trimethylsilylethyl (Teoc) and benzyl carbamate (Cbz or Z), more preferably Fmoc or Z.

The term "carboxyl-protecting group" is used herein in its broadest sense and refers to any group capable of protecting a carboxyl group such as those disclosed in Green, T.W., "*Protective Groups in Organic Synthesis*" John Wiley & Sons, New York 1991, pp 224-276, the contents of which are incorporated herein by

reference.

The term "histidine protecting group" is used herein in its broadest sense and refers to any group capable of protecting a histidine group such as carbamates or sulphonyl groups for example Z, tosyl or mesyl.

The term "phenol protecting group" is used herein in its broadest sense and refers to any group capable of protecting a phenol group in particular a tyrosine phenol group for example 2,4-DNP, acyl, alkyl or benzyl.

The salts of the compound of Formula I, II or III are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts include salts of pharmaceutically acceptable cations such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium; acid addition salts of pharmaceutically acceptable inorganic acids such as hydrochloric, orthophosphoric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic and hydrobromic acids; or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, trihalomethanesulphonic, toluenesulphonic, benzenesulphonic, salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

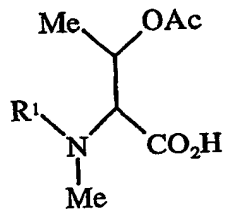
By "derivative" is meant any salt, hydrate, protected form or any other compound which is capable of

providing (directly or indirectly) a compound of Formula I or II. Preferably the derivative is pharmaceutically acceptable.

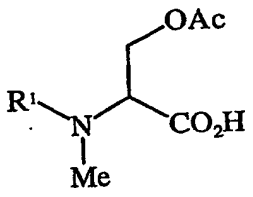
The term "tautomer" is used herein in its broadest sense to include compounds of Formula I or II which are capable of existing in a state of equilibrium between two isomeric forms. Such compounds may differ in the bond connecting two atoms or groups and the position of these atoms or groups in the compound.

The term "isomer" is used herein in its broadest sense and includes structural, geometric and stereo isomers. As the compound of Formula I or II may have one or more chiral centres, it is capable of existing in enantiomeric forms.

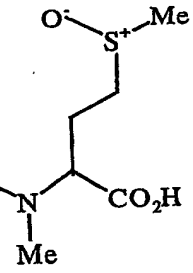
Representative examples of compounds of formula I are as follows:



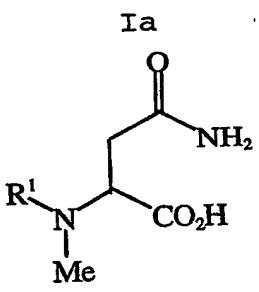
Ia



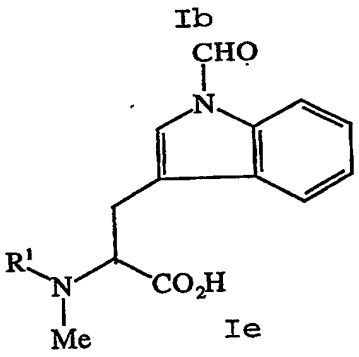
Ib



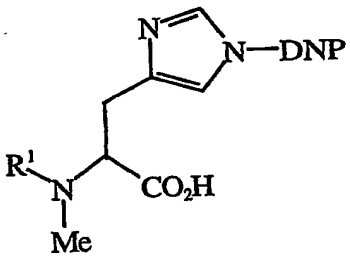
Ic



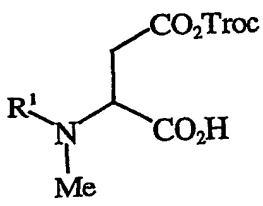
Id



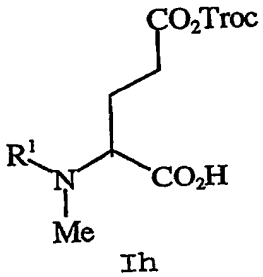
Ie



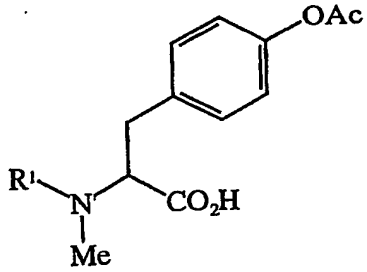
If



Ig



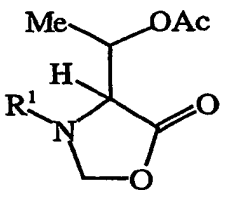
Ih



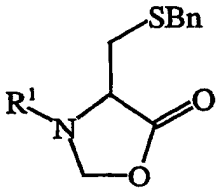
Ii

Compounds Ia and Ib are present as dicyclohexylammonium (DCHA) salts, Id is chiral and R^1 is as defined above.

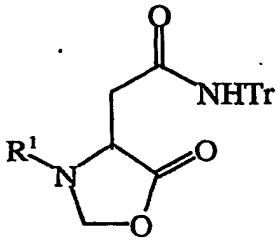
Representative examples of compounds of formula II are as follows:



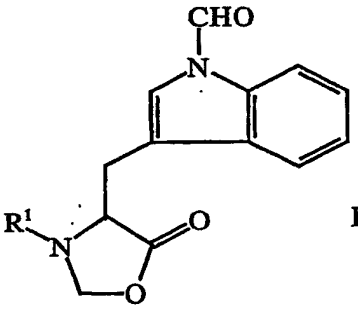
IIa



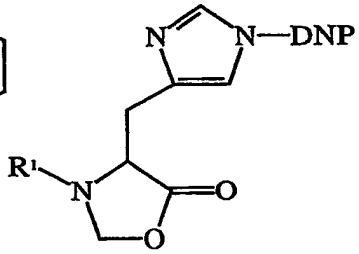
IIb



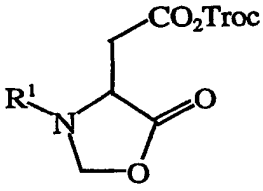
IIc



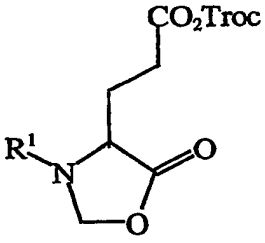
IId



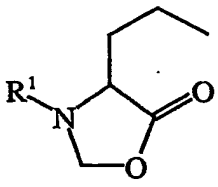
IIe



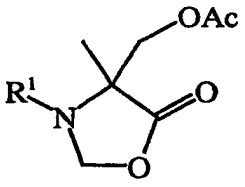
IIf



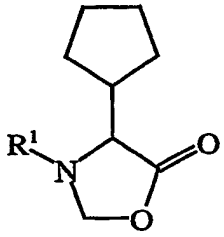
IIg



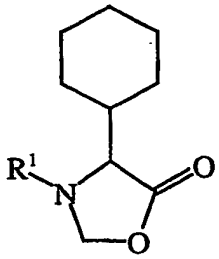
IIh



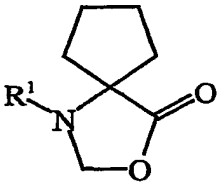
Iii



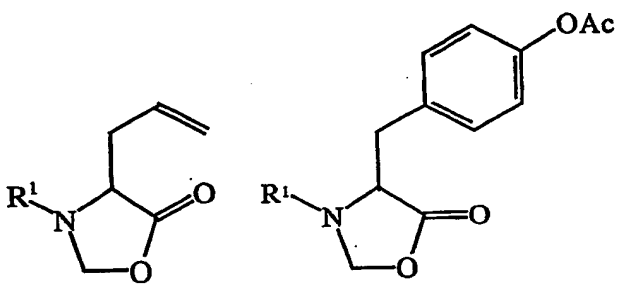
IIj



IIk



Iil



IIm IIn

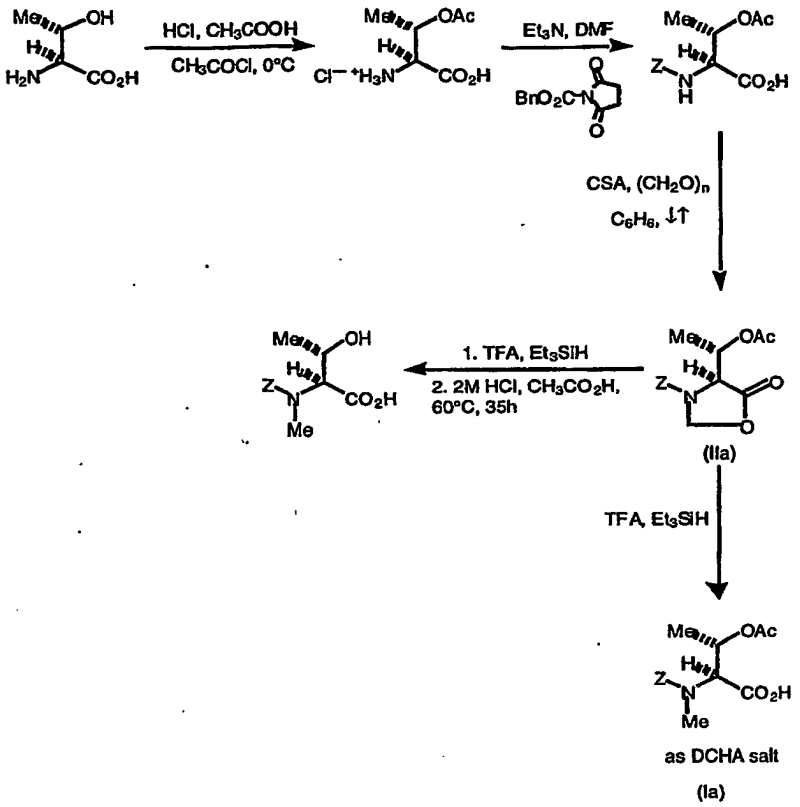
The reductive cleavage may be performed using any suitable known technique, preferably the method described by Freidinger *et al*[28] which employs trifluoroacetic acid (TFA) as the acid and triethylsilane (Et_3SiH) as the reductant.

Conversion step (a) results in the protection of the amino group on the compound of formula III to produce a compound of formula IV. This step may be performed using any suitable known technique, such as those disclosed in Greene, T.W., "*Protective Groups in Organic Synthesis*" John Wiley & Sons, New York, 1991.

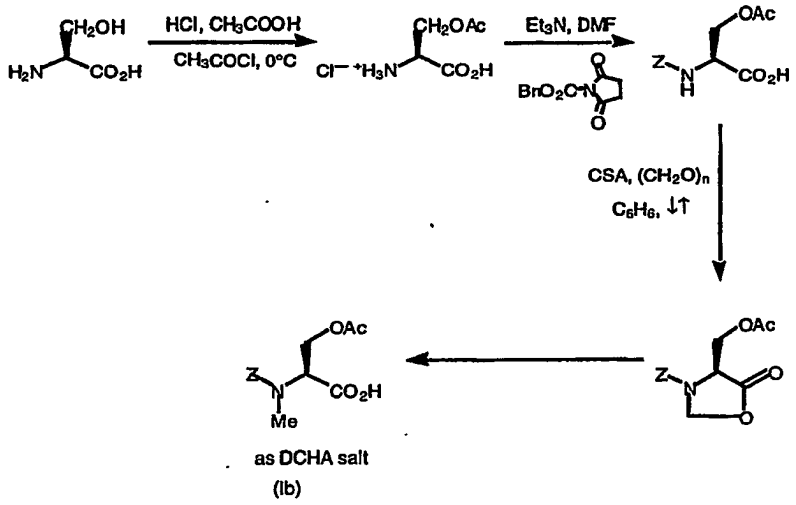
Step (b) results in cyclisation of the compound of formula IV using any suitable known technique such as described by Aurelio, L. *et al*[27] using a formaldehyde source for example paraformaldehyde and paratoluenesulphonic acid (TsOH) in a suitable organic solvent such as benzene or toluene.

The preferred preparations of compounds (Ia) to (IIn) described above are shown in Schemes 1 to 9a below.

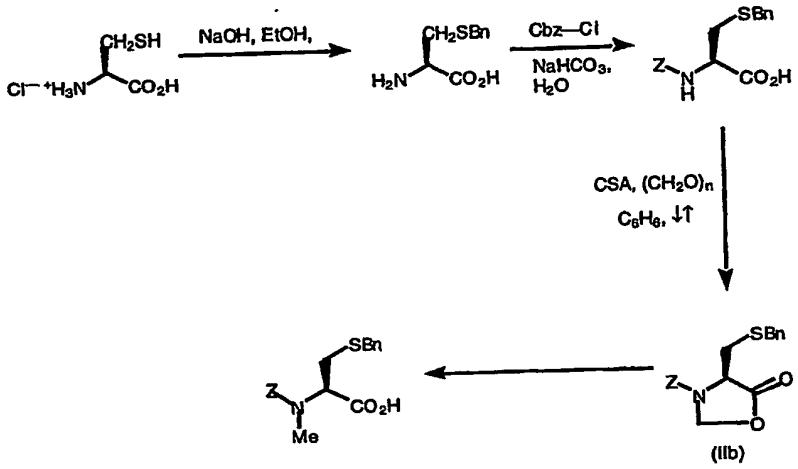
Scheme 1 - Compounds (Ia) and (IIa)



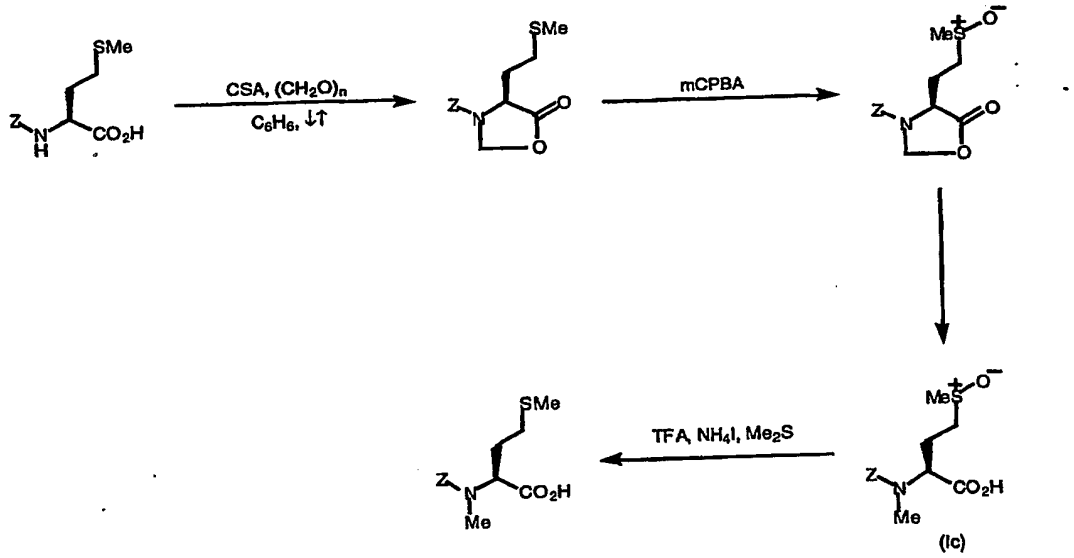
Scheme 2 - Compound (Ib)



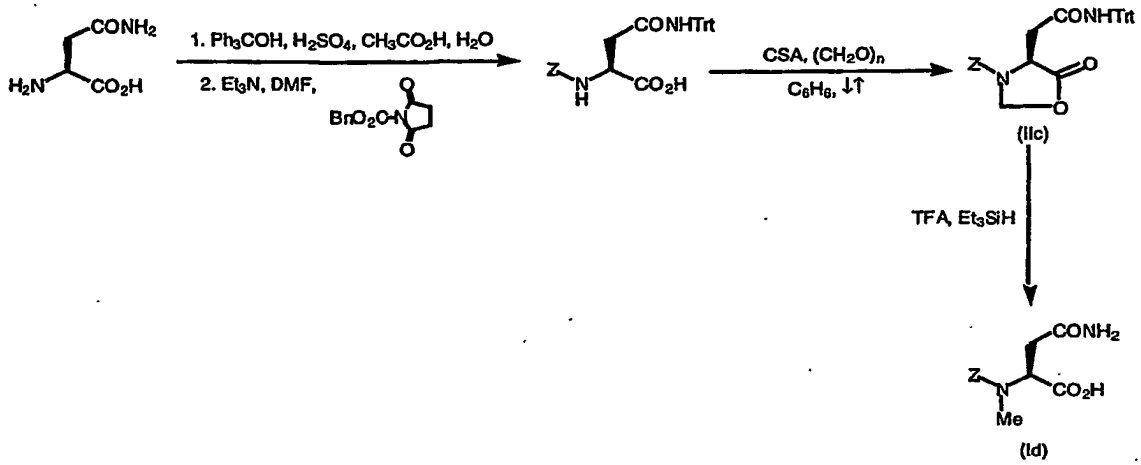
Scheme 3 - Compound (IIb)



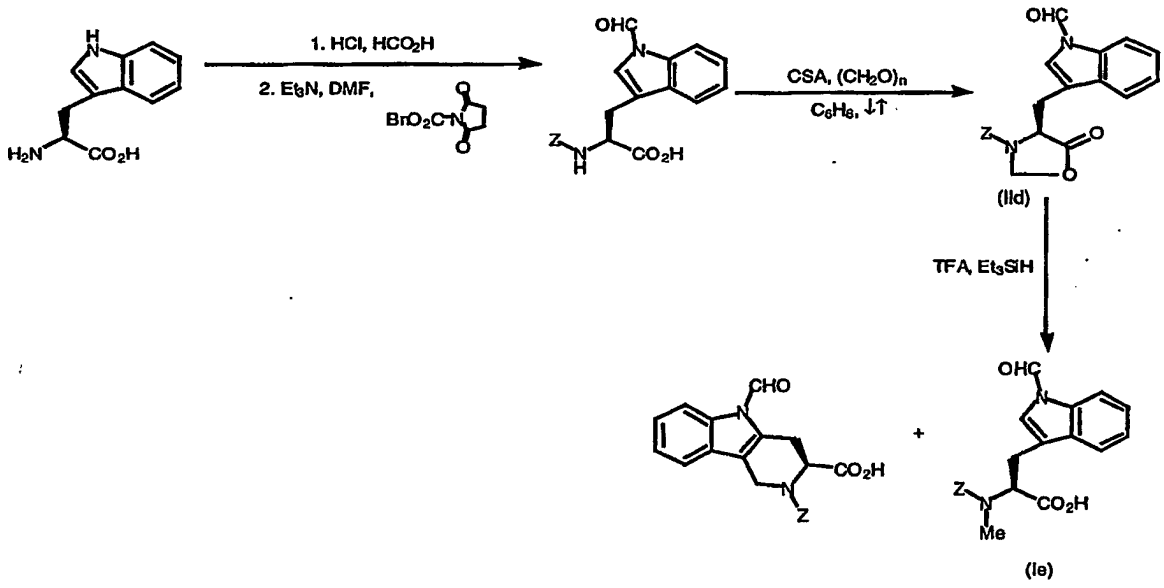
Scheme 4 - Compound (Ic)



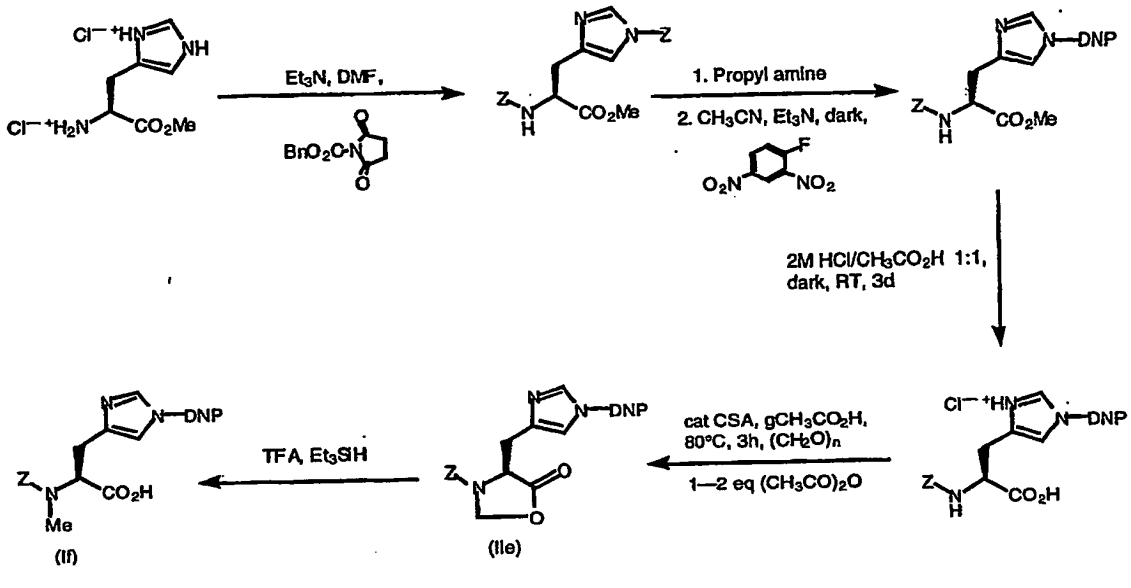
Scheme 5 - Compounds (IIc) and (Id)



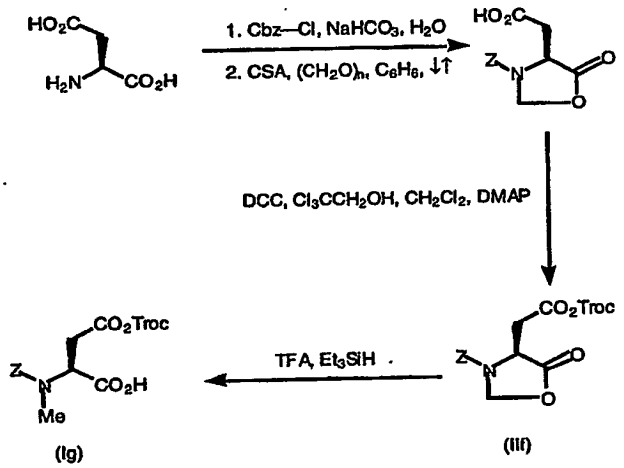
Scheme 6 - Compounds (Ie) and (IId)



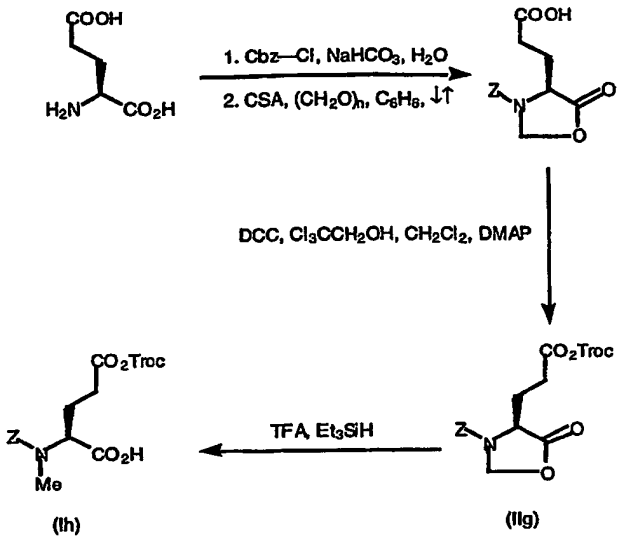
Scheme 7 - Compounds (If) and (IIe)



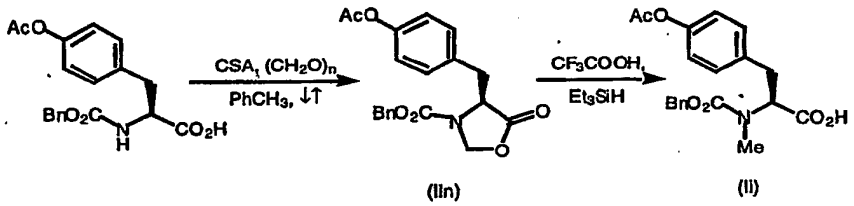
Scheme 8 - Compounds (Ig) and (IIf)



Scheme 9 - Compounds (Ih) and (IIg)



Scheme 9a - Compounds (Ii) and (IIn)



The term "peptide" is used herein in its broadest sense and refers to a compound formed by linking amino acids with amide bonds, using the amino group of one molecule and the carboxyl group in another. The peptide may be a dipeptide containing two amino acid residues, a tripeptide containing three amino acid residues and so on up to oligopeptides which contain relatively short chains of several amino acid residues and longer polymers which are polypeptides or proteins.

EXAMPLES

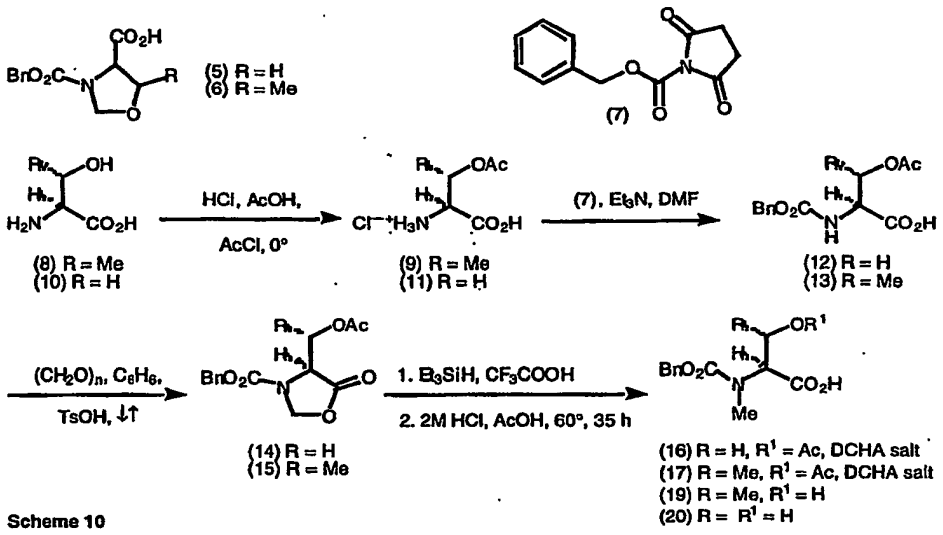
The invention will now be described with reference to the following examples. These examples are not to be construed as limiting the invention in any way.

All melting points are uncorrected and were recorded on a Reichert "Thermopan" microscope hot-stage apparatus. Infrared spectra were recorded on a Perkin-Elmer 1720X FTIR spectrometer, using a diffuse reflectance accessory with KBr background. N.m.r. spectra including the DEPT experiments were recorded in (D)chloroform solution unless otherwise stated on a Brüker AM-300 Spectrometer (^{1}H at 300.13 MHz and ^{13}C at 75.47 MHz) or on a Brüker DRX 400 MHz machine. Chemical shifts are reported as δ values in parts per million (ppm) and coupling constants (J) in Hz relative to residual solvent. Electrospray mass spectra (e.s.m.s.) were obtained on a VG Bio-Q triple quadrupole mass spectrometer using water/methanol/acetic acid (0:99:1 or 50:50:1) mixtures as the mobile phase. Low resolution mass spectra (e.i.) were performed on a Shimadzu GCMS-QP5050A mass spectrometer fitted with a direct insertion probe at 70 eV, with a transfer line temperature of 250°C. Other low and high resolution mass spectra (l.s.i.m.s.) were measured on a Kratos concept mass spectrometer at 70 eV with a source temperature of 200°C. Optical rotations were obtained on a Perkin-Elmer 141 Polarimeter. "Flash column chromatography" was carried out using silica gel (silica gel 60, 230-400 mesh ASTM) supplied by Merck Chemicals (Darmstadt). Ethyl acetate and hexane used for chromatography were distilled prior to use. All solvents were purified by distillation. For dry solvents, procedures from Perrin and Armarego[29] were followed. Dry dichloromethane was distilled and stored over Linde type 4Å molecular sieves. All other reagents and solvents were purified or dried as described by Perrin and Armarego.[29]

Example 1 Serine, Threonine and Tyrosine

The formation of the 5-oxazolidinones of serine and threonine is complicated by participation of the sidechain hydroxyls to form oxazolidines like structures

(5) and (6). In the case of threonine, this intermediate was also produced in the attempted reductive cleavage[27]. Thus, sidechain protection was required and several strategies were considered.



Scheme 10

Reddy *et al.*[30] have prepared the *tert*-butyldiphenylsilyl ether of serine. The use of this silyl ether was deemed too expensive for present purposes. The *tert*-butyl ethers of serine and threonine were also attractive possibilities but were discounted on the basis that the TFA/Et_3SiH reductive cleavage would result in deprotection of the *tert*-butyl ether. This de-etherification would not be commensurate with the subsequent incorporation of the serine or threonine unit into oligopeptides. A number of authors report methods for the formation of *O*-benzyl serine and threonine.[31-33] The expense of some of these procedures or their lack of reproducibility made them less enticing. In the end, the simple expedient of acetylation fulfilled all the objectives. L-Threonine (8) was used to prepare *O*-acetyl threonine (9) in high yield according to the method of Wilchek and Patchornik (Scheme 10).[34] This procedure was equally successful with L-serine (10) in providing the acetate (11).

The formation of the 5-oxazolidinones using the intermediates (12) and (13) proceeded in high yield to give the desired compounds (14) (87%) and (15) (91%). Reductive cleavage gave the *N*-methyl-*O*-acetyl amino acids (16) (74%) and (17) (80%) as their dicyclohexylamine salts. These acetates are in suitable form for use in solution and solid phase coupling procedures but the question of deprotection remained. Removal of the acetate esters under basic conditions has been reported in relation to serine derivatives[35] but was unsuccessful in this study with the threonine acetate (17). Attempted base hydrolyses of the threonine acetate (17) always resulted in isolation of the starting material and this was attributed to the *in situ* formation of the tetrahedral intermediate (18) (Figure 2) which survived the hydrolytic conditions and returned the starting material upon acidic work-up.

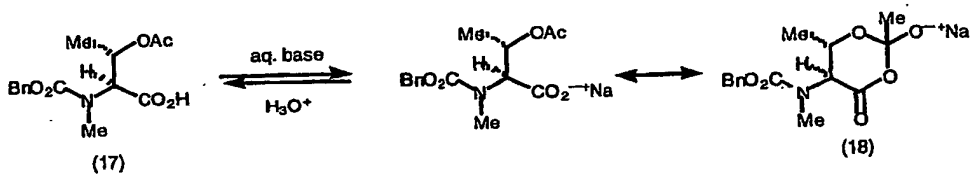
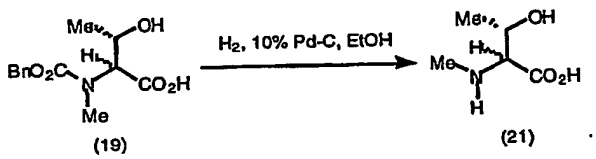


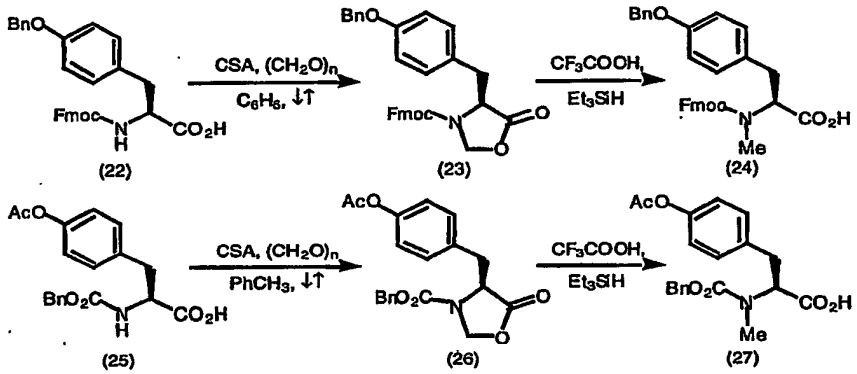
Figure 2

Conversely, aqueous acidic conditions and mild heating (Scheme 10) removed the acetate in high yield to give the alcohol (19) (97%). The same sequence of reactions works well for the serine intermediates (14), (16) and (20). Confirmation that this synthetic sequence did not reduce the optical purity was obtained by hydrogenolysis of the threonine carbamate (19) (Scheme 11). The isolated *N*-methyl-L-Threonine (21) had an optical rotation of $[\alpha]_D$ -14° (*c* = 1, 6M HCl) which matched previously reported values.[28] Thus, *N*-methyl serine and threonine are available with and without sidechain protection.



Scheme 11

Tyrosine forms the expected oxazolidinone without sidechain protection but the yields for its formation (37%) and subsequent reductive cleavage (60%) are lower than desired. Given the success of sidechain acetylation in the serine and threonine manipulations, a similar strategy was attempted with tyrosine. Solubility problems were encountered with both the Fmoc and benzyl carbamates of tyrosine and their conversion to the corresponding acetates. The commercially available tyrosine benzyl ether (22) suited the oxazolidinone chemistry. The oxazolidinone (23) was isolated in 74% yield (Scheme 12). Reductive cleavage then gave the *N*-methyl tyrosine (24) in 70% yield: a substantial improvement in comparison to the previous sequence in which the hydroxy group was unprotected.



Scheme 12

The tyrosine benzyl carbamate (25)[36] was also converted to the oxazolidinone (26) (89%). The reductive cleavage afforded the *N*-methyl tyrosine *O*-acetate (27) (70%). Formation of the *N*-methyl tyrosine (27) represents a 40% improvement compared to the tyrosine sequence in which the hydroxy group was unprotected and it is the most efficient procedure we have devised for tyrosine.

(S)-3-Benzyloxycarbonyl-4-acetoxymethyloxazolidin-5-one (14)

To a sample of the carbamate (12) (1.11 g, 4.0 mmol) in toluene (50 ml) was added camphorsulfonic acid

(70 mg) and dry paraformaldehyde (1.0 g). The reaction mixture was then heated to reflux for 30-60 mins [monitored by TLC (40% ethyl acetate-hexane)]. The mixture was cooled, filtered to remove solids and diluted with ether (150 ml). The ethereal solution was washed with 2.5% aqueous sodium bicarbonate solution (4 x 30 ml). The combined aqueous layers were extracted with ether (30 ml) and the combined ethereal layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the oxazolidinone (14) as an oil (1.01 g, 87%). A small sample was further purified by flash chromatography on silica eluting with 30% ethyl acetate-hexane (Found: C, 57.54; H, 5.26; N, 4.96. $C_{14}H_{15}NO_6$ requires C, 57.34; H, 5.16; N, 4.78%). $[\alpha]_D^{24}$ +110.7° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3090, 3065, 3034 and 3010 (CH, aromatic), 3000-2900 (CH, saturated), 1807 (C=O, oxazolidinone), 1746 (C=O, acetate), 1719 (C=O, carbamate), 1500, 1452, 1419, 1359, 1315, 1290, 1234, 1170, 1130, 1060, 1034, 969, 945, 765, 699. δ_H 7.33, s, 5H, ArH; 5.51, bs, 1H, NC**H**HO; 5.20, d, *J* 3.8 Hz, 1H, NCH**H**O; 5.16, s, 2H, $ArCH_2$; 4.61-4.58, m, 1H, NCHCO; 4.42-4.32, m, 2H, $C\mathbf{H}_2OAc$; 1.99, s, 3H, $COCH_3$. δ_C 169.85, 2 x CO; 152.30, OCON; 135.07, quaternary ArC; 128.57, 128.25, 5 x ArC; 78.39, C2; 68.04, $ArCH_2$; 62.19, $\mathbf{C}H_2OAc$; 54.41, C4; 20.44, $COCH_3$.

(4S)-3-Benzyloxycarbonyl-4-[(1S)-acetoxyethyl]oxazolidin-5-one (15)

To a sample of the carbamate (13) (1.47 g, 5 mmol) in toluene (50 ml) was added camphorsulfonic acid (70 mg) and dry paraformaldehyde (1.0 g). The reaction mixture was then heated to reflux for 30-60 mins [monitored by TLC (40% ethyl acetate-hexane)]. The mixture was cooled, filtered to remove solids and diluted with ether (150 ml). The ethereal solution was washed with 2.5% aqueous sodium bicarbonate solution (4 x 30 ml). The combined aqueous layers were extracted with ether (30 ml) and the combined ethereal layers were dried ($MgSO_4$),

filtered and concentrated *in vacuo* to give the oxazolidinone (15) as an oil (1.38 g, 91%). A small sample was further purified by flash chromatography on silica eluting with 30% ethyl acetate-hexane; (Found: C, 58.62; H, 5.63; N, 4.71. $C_{15}H_{17}NO_6$ requires C, 58.63; H, 5.58; N, 4.56%). (Found: M+H, 308.1142. $C_{15}H_{18}NO_6$ requires 308.1134). +120.7° (*c*, 2.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3092, 3066 and 3033 (CH, aromatic), 3000-2900 (CH, saturated), 1808 (C=O, oxazolidinone), 1742 (C=O, acetate), 1719 (C=O, carbamate), 1498, 1454, 1409, 1360, 1328, 1232, 1169, 1124, 1041, 955, 897, 753, 700. δ_H 7.32, s, 5H, ArH; 5.70, bs, 1H, C**H**OAc; 5.29-5.18, m, 4H, NCH_2O and $ArCH_2$; 4.41, bs, 1H, NCHCO; 1.97, s, 3H, $COCH_3$, 1.34-1.31, m, 3H, $CHCH_3$. δ_C 170.14 and 169.19, 2 x CO; 153.83, OCON; 134.98, quaternary ArC; 128.59, 128.37, 5 x ArC; 78.98, C2; 70.59, **C**HOAc; 68.34, $ArCH_2$; 59.11, C4; 20.76, $COCH_3$; 16.63, CH_3CH. *m/z* (l.s.i.m.s.) 308 (M+H, 90%), 289, (50), 264 (100).

N-*Benzyloxycarbonyl*-N-*methyl*-L-*serine*-O-*acetate (16)*

A sample of the oxazolidinone (14) (1.18 g, 4.0 mmol) was dissolved in chloroform (20 ml) at room temperature and triethylsilane (1.89 ml) was added followed by trifluoroacetic acid (20 ml) and the reaction mixture was left to stand for 3-4 d. The reaction mixture was concentrated under reduced pressure. To the residue was added toluene (50 ml) and the mixture was again concentrated *in vacuo*. This procedure was repeated with more toluene (50 ml). The residue was then diluted with ether and extracted with saturated aqueous sodium bicarbonate solution (4 x 30 ml). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 5 M hydrochloric acid. The aqueous phase was then extracted with ether (3 x 50 ml). The combined ethereal extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to approximately 20 ml volume. Dicyclohexylamine (DCHA) (0.8 ml) was added and any solid,

which formed immediately, was filtered off. The clear filtrate was left to stand overnight during which the *N*-methyl serine acetate (16) precipitated as its DCHA salt (1.40 g, 74%) m.p. 135-147° (Found: C, 65.52; H, 8.65; N, 5.86. $C_{26}H_{40}N_2O_6$ requires C, 65.52; H, 8.46; N, 5.88%). -8.0° (*c*, 2.0 in $CHCl_3$). ν_{max} (KBr disk)/cm^{-1} 3062, 3034 and 3005 (CH, aromatic), 3000-2800 (CH, saturated), 2476 and 2417 (NH_2^+), 1738 (C=O, acetate), 1693 (C=O, carbamate), 1641 (CO_2^-), 1566, 1441, 1392, 1370, 1345, 1312, 1286, 1250, 1149, 1075, 696. δ_H 9.15, bs, 2H, NH_2^+; 7.33-7.24, m, 5H, ArH; 5.21-4.99, m, 2H, $ArCH_2$; 4.84, td, *J* 10.0 and 4.2 Hz, 1H, NCHCO; 4.55, dt, *J* 11.8 and 3.8 Hz, 1H, CHHOAc; 4.42-4.26, m, 1H, CHHOAc; 2.97-2.88, m, 5H, NCH_3 and CHNCH; 1.97-1.13, m, 23H, 10 x CH_2 and $COCH_3$. δ_C (rotamers) 172.30, 172.14 and 170.85 (2 x C=O); 156.97 and 156.77 (C=O, carbamate); 137.01 (quaternary ArC); 128.37, 127.81, 127.58 and 127.52 (5 x ArC); 66.97 and 66.89 ($ArCH_2$); 62.54 and 62.48 ($CHCH_2O$); 59.99 and 59.75 (CHNCH); 52.75 (NCHCO); 31.14 (NCH_3); 28.95, 25.04 and 24.67 (10 x CH_2); 20.83 and 20.74 ($COCH_3$).

N-Benzyloxycarbonyl-N-methyl-L-threonine-O-acetate (17)

A sample of the oxazolidinone (15) (1.22 g, 4.0 mmol) was dissolved in chloroform (20 ml) at room temperature and triethylsilane (1.89 ml) was added followed by trifluoroacetic acid (20 ml) and the reaction mixture was left to stand for 3-4 d. The reaction mixture was concentrated under reduced pressure. To the residue was added toluene (50 ml) and the mixture was again concentrated *in vacuo*. This procedure was repeated with more toluene (50 ml). The residue was then diluted with ether and extracted with saturated aqueous sodium bicarbonate solution (4 x 30 ml). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 5 M hydrochloric acid. The aqueous phase was then extracted with ether (3 x 50 ml). The combined ethereal extracts were dried ($MgSO_4$), filtered and evaporated under

reduced pressure to approximately 20 ml volume. Dicyclohexylamine (DCHA) (0.8 ml) was added and any solid, which formed immediately, was filtered off. The filtrate solution was left to stand overnight during which the *N*-methyl threonine acetate (17) precipitated as its DCHA salt (1.57 g, 80%) m.p. 121-124° (Found: C, 66.05; H, 8.74; N, 5.49. $C_{27}H_{42}N_2O_6$ requires C, 66.10; H, 8.63; N, 5.71%). $[\alpha]_D^{25}$ +5.6° (*c*, 1.0 in $CHCl_3$). ν_{max} (KBr disk)/cm^{-1} 3200-2800 (CH, saturated), 2525 and 2456 (NH_2^+), 1729 (C=O, acetate), 1704 (C=O, carbamate), 1625 (CO_2^-), 1570, 1496, 1453, 1372, 1308, 1249, 1203, 1178, 1160, 1140, 1100, 1055, 735. δ_H (rotamers) 9.50, bs, 2H, NH_2^+; 7.33-7.24, m, 5H, ArH; 5.51-5.43, quintet, *J* 6.5 Hz, 1H, C**H**OAc); 5.22-4.99, m, 2H, $ArCH_2$; 4.68 and 4.57, 2d, *J* 6.7 Hz, 1H, NCHCO; 2.99-2.87, m, 5H, NCH_3 and CHNCH; 1.94-1.02, m, 26H, 10 x CH_2 and $COCH_3$ and CH_3CH. δ_C (rotamers) 172.27, 172.15 and 169.94 (2 x C=O); 157.34 and 156.90 (C=O, carbamate); 137.04 and 136.94 (quaternary ArC); 128.35, 127.79 and 127.60 (5 x ArC); 70.37 and 69.94 (**C**HOAc); 67.70 and 66.92 ($ArCH_2$); 64.32 (CHNCH); 52.45 (NCHCO); 32.03 and 31.79 (NCH_3); 28.84, 28.79, 25.06 and 24.65 (10 x CH_2); 22.05 ($CO\mathbf{C}H_3$); 17.81 and 17.66 ($\mathbf{C}H_3CH$).

N-Benzyloxycarbonyl-N-methyl-L-serine (19)

A sample of the serine DCHA salt (16) (970 mg, 2.0 mmol) was suspended in a mixture of glacial acetic acid and 2M hydrochloric acid (20 ml, 1:1) with stirring. The mixture was then heated to 60°C for *ca.* 30 h (TLC). The reaction mixture was then diluted with water (300 ml) and extracted with ether (3 x 100 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated at reduced pressure to give the *N*-methyl serine (19) as an oil (480 mg, 95%), which was identical in all respects with previously reported material.[28]

N-Benzyloxycarbonyl-N-methyl-L-threonine (20)

A sample of the threonine DCHA salt (17) (1.04 g, 2.0 mmol) was suspended in a mixture of glacial acetic acid and 2M hydrochloric acid (20 ml, 1:1) with stirring. The mixture was then heated to 60°C for *ca.* 30 h (TLC). The reaction mixture was then diluted with water (300 ml) and extracted with ether (3 x 100 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated at reduced pressure to give the *N*-methyl threonine (20) as an oil (520 mg, 97%), which was identical in all respects with previously reported material.[28]

N-Methyl-L-threonine (21)

A small sample of the carbamate (19) was hydrogenolysed over 10% palladium on charcoal catalyst.[28] The material isolated had $[\alpha]_D^{25}$ -14° (*c*, 0.5 in 6 M HCl) which was identical to authentic material.[28]

(S)-3-(Carbonyl-9H-fluoren-9-ylmethoxy)-4-(4-benzyloxybenzyl)-oxazolidin-5-one (23)

To a sample of the carbamate (22) (470 mg, 0.9 mmol) in toluene (150 ml) was added camphorsulfonic acid (66 mg). The reaction mixture was then heated to reflux for 4 h during which dry paraformaldehyde (500 mg) was added in small portions down the condenser. The mixture was then cooled, filtered to remove solids and the filtrate was evaporated under reduced pressure. The residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution (3 x 30 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica eluting with 25% ethyl acetate-hexane to give the oxazolidinone (23) as a foam (405 mg, 86%); (Found: M^+, 505.1891. Calc. for $C_{32}H_{27}NO_5$: M^+, 505.1968). $[\alpha]_D^{22}$ +132.5° (*c*, 1.0 in Et_2O). ν_{max} (KBr disk)/cm^{-1} 3034 (CH, aromatic), 3000-2800 (CH, saturated),

1800 (C=O, oxazolidinone), 1717 (C=O, carbamate), 1610, 1511, 1451, 1422, 1357, 1300, 1242, 1177, 1159, 1129, 1052, 1024, 830, 759, 741, 696. δ_H (rotamers) 7.77-6.60, m, 17H, ArH; 5.11, brs, 1H, NCHHO; 4.99-4.95, m, 1H, OCHHCH; 4.73-4.64, m, 1H, OCHHCH; 4.47, m, 0.5H, NCHCO; 4.27-4.19, m, 1H, OCH_2CH; 4.10, m, 1H, NCHHO; 3.94, m, 0.5H, NCHCO; 3.32-2.35, m, 2H, $NCHCH_2$. δ_C (rotamers) 171.54 (C=O); 157.84 (C=O, carbamate); 151.84, 143.09, 141.12, 136.50 and 126.19 (quaternary ArC); 130.31, 128.25, 127.67, 127.17, 126.93, 124.20, 119.87, 119.80 and 114.76 (ArC); 77.49 (NCH_2O); 69.56 ($ArCH_2$); 67.10 and 66.31 (OCH_2CH); 56.05 (NCHCO); 46.93 (OCH_2CH); 34.20 ($ArCH_2CH$).

(S)-3-Benzyloxycarbonyl-4-(4-acetoxybenzyl)-oxazolidin-5-one (26)

To a sample of the carbamate (25) (2.90 g, 7.9 mmol) in toluene (50 ml) was added camphorsulfonic acid (200 mg). To the reaction mixture was added dry paraformaldehyde (3.0 g) and the mixture was heated to reflux for 1 h. The mixture was then cooled, filtered to remove solids and the filtrate was evaporated under reduced pressure. The residue was taken up in ether (100 ml). The ether layer was washed with 5% sodium carbonate solution (3 x 50 ml) followed by water and then brine. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue (2.80 g) was purified by flash chromatography on silica eluting with 20% ethyl acetate-hexane to give the oxazolidinone (26) as a clear colourless oil (2.61 g, 89%); (Found: C, 64.89; H, 5.35; N, 3.87. $C_{20}H_{19}NO_6$ requires C, 65.03; H, 5.18; N, 3.79%.) $[\alpha]_D^{24}$ +172.3° (*c*, 1.0 in $CHCl_3$). ν_{max} (NaCl)/cm^{-1} 3100, 3062 and 3034 (CH, aromatic), 3000-2800 (CH, saturated), 1800 (C=O, oxazolidinone), 1760 (C=O, acetate), 1716 (C=O, carbamate), 1604, 1506, 1416, 1361, 1310, 1202, 1126, 1049, 1013, 912, 843, 754. δ_H 7.35-7.29 and 7.21-6.91, 2m, 9H, ArH; 5.28-5.14, m, 3H, $ArCH_2$ and NCHHO; 4.49, brs, 1H, H4; 4.32, d, *J* 3.9 Hz, 1H, NCHHO; 3.42-3.08, m, 2H, $CHCH_2$;

2.23, s, 3H, CH_3. δ_C 171.51 and 168.95 (C=O); 152.06 (C=O, carbamate); 149.93 (C5'), 135.37 and 131.91 (quaternary ArC); 130.42, 128.51, 128.25, 121.70 (ArC); 77.78 (C2); 67.62 ($ArCH_2$); 56.11 (C4); 35.33 and 34.31 ($CHCH_2$), 20.85 (CH_3).

N-(Carbonyl-9H-fluoren-9-ylmethoxy)-N-methyl-L-tyrosine-O-benzyl ether (24)

A sample of the oxazolidinone (23) (95 mg, 0.2 mmol) was dissolved in dichloromethane (5 ml) at room temperature and triethylsilane (270 µl, 1.7 mmol) was added followed by trifluoroacetic acid (1.2 ml, 10.5 mmol) and the reaction mixture was left to stand for 2 d. The reaction mixture was concentrated under reduced pressure. To the residue was added dichloromethane (5 ml) and the mixture was again concentrated *in vacuo*. This procedure was repeated with toluene (5 ml) until traces of trifluoroacetic acid were removed. The residue was then diluted with ethyl acetate and extracted with saturated aqueous sodium bicarbonate solution (3 x 30 ml). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 2 M hydrochloric acid. The aqueous phase was then extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with 95:4:1 dichloromethane/methanol/acetic acid to yield the *N*-methyl acid (24) as a white foam (67 mg, 70%) $[\alpha]_D^{24}$ -1.6° (*c*, 0.5 in Et_2O). R_f 0.3 (95:4:1 dichloromethane/methanol/acetic acid). δ_H (rotamers) 7.74-6.46, m, 17H, ArH; 4.90-4.07, m, 6H, $ArCH_2O$ and $CHCH_2O$ and NCH; 3.27, dd, *J* 4.8 and 14.4 Hz, 1H, and 3.08-2.96, m, and 2.66-2.63, m, 2H, $ArCH_2CH$; 2.78 and 2.74, 2s, NCH_3. δ_C (rotamers) 174.21, C=O; 156.70, OCON; 155.85, 154.28, 143.41, 143.31 and 140.93, quaternary ArC; 129.57, ArC; 128.24, quaternary ArC; 127.55, 126.73, 124.64, 124.31, 119.62 and 115.20, ArC;

67.62 and 67.10, $ArCH_2O$; 60.59 and 60.26, NCHCO; 46.81 and 46.69, OCH_2CH; 33.61 and 33.46, $ArylCH_2CH$; 31.92, NCH_3.

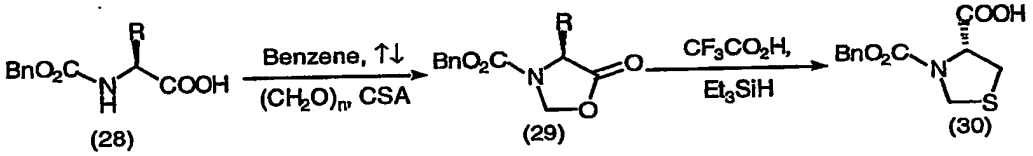
N-Benzyloxycarbonyl-N-methyl-L-tyrosine-O-acetate (27)

A sample of the oxazolidinone (26) (1.50 g, 4.1 mmol) was dissolved in chloroform (20 ml) at room temperature and triethylsilane (1.9 ml) was added followed by trifluoroacetic acid (20 ml) and the reaction mixture was left to stand for 4 d. The reaction mixture was diluted with toluene and concentrated under reduced pressure. This procedure was repeated with a further aliquot of toluene (50 ml). The residue was then diluted with ether and extracted with 5% sodium carbonate solution (4 x 20 ml). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 5 M hydrochloric acid. The aqueous phase was then extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford a clear oil (1.33 g, 88%). A sample of the oil was converted to the t-butylamine salt by dissolution in ether and addition of t-butylamine (1.1 equiv.) followed by hexane until the solution turned slightly cloudy. The turbid solution was then left to stand at room temperature for 4 h and then at 0°C overnight during which the *N*-methyl tyrosine acetate (27) precipitated as its t-butylammonium salt m.p. 54-60°C (Found: C, 64.71; H, 7.39; N, 6.41. $C_{24}H_{32}N_2O_6$ requires C, 64.85; H, 7.26; N, 6.30%). $[\alpha]_D^{24}$ -34.3° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr disk) 3121, 3064 and 3033 (CH, aromatic), 3000-2800 (CH, saturated), 2622 and 2529, $^+NH_3$, 1760 (C=O, acetate), 1674 (C=O, carbamate), 1592 (CO_2^-), 1507, 1448, 1377, 1314, 1209, 1194, 1134, 750, 695, 639. δ_H (rotamers) 7.74, brs, 3H, $^+NH_3$; 7.29-6.88, m, 9H, ArH; 5.01-4.64, m, 3H, $ArCH_2O$ and NCHCO; 3.38-3.28 and 3.00-2.77, 2m, 5H, $NCHCH_2$ and NCH_3; 2.26, s, 3H, $COCH_3$; 1.23, s, 9H, $C(CH_3)_3$. δ_C (rotamers) 175.95, C=O; 169.51, C=O; 156.89 and 156.50, OCON; 148.99, 136.78, 136.66, 136.60 and 136.50,

quaternary ArC; 129.68, 128.39, 127.76, 127.45 and 121.32, ArC; 66.97 and 66.86, $ArCH_2O$; 62.64 and 62.34, NCHCO; 51.23, $\mathbf{C}(CH_3)_3$; 35.51 and 35.05, $NCH\mathbf{C}H_2$; 31.90 and 31.08, NCH_3; 27.51, $C(CH_3)_3$; 21.10, $COCH_3$.

Example 2 Cysteine and Cystine

The sulfur bearing amino acids have given mixed results using 5-oxazolidinones (Figure 3).[28] The cysteine carbamate (28a) gave the oxazolidinone (29a) in only 3% yield. Methionine, on the other hand, gave the oxazolidinone (28b) in 91%. The reductive cleavage of the oxazolidinone (28a) gave the thiazolidine (30) exclusively indicating the requisite iminium ion was forming and being intercepted intramolecularly by the thiol. The methionine intermediate (28b) gave a mixture of products.



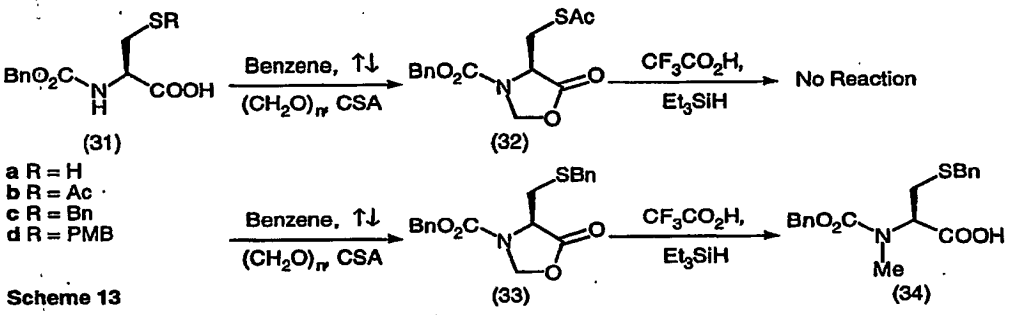
a R = CH_2SH
b R = $CH_2CH_2SCH_3$

Figure 3

In order to lessen to nucleophilicity of the thiol, the *S*-acetyl cysteine derivative (31b)[37,38] was prepared and this underwent oxazolidination in moderate yield (51%) (Scheme 13). However, attempted reductive cleavage of the oxazolidinone (32) gave no *N*-methyl products upon work-up. Thus the *S*-benzyl cysteine (31c)[39] was converted to the oxazolidinone (33) high yield (89%) and subsequent reductive cleavage with trifluoroacetic acid and triethylsilane gave the expected *N*-methyl amino acid (34). Removal of the *S*-benzyl group in any subsequent sequence may present problems given the preferred method for debenzylation involves treatment with HF.[38] Thus the *S*-PMB (paramethoxybenzyl) acid (31d) was proposed, as the ultimate removal of the PMB ether can be effected with refluxing trifluoroacetic acid.[40]

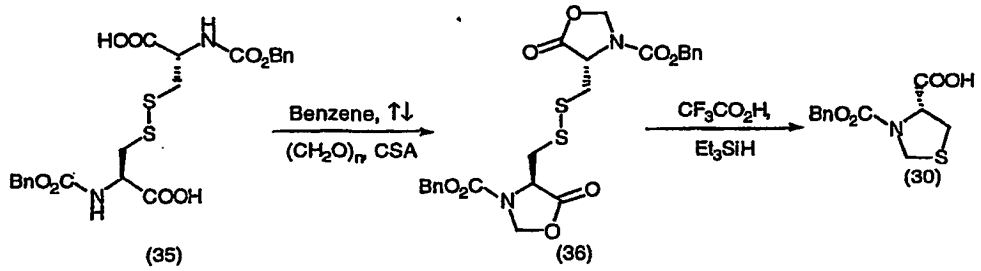
Unfortunately, all attempts to convert the PMB ether (31d) to the corresponding oxazolidinone resulted in decomposition.

However, the formation of *N*-methyl cysteine is performed efficiently by the related method of Yamashiro *et al.*[39] Their method involves the reaction of cysteine with paraformaldehyde to give a thiazolidine carboxylic acid. A dissolving metal reductive cleavage of the thiazolidine ring generates *N*-methyl cysteine, which can then be converted in many ways to a range of synthetically useful intermediates including the *S*-benzyl carbamate (34).



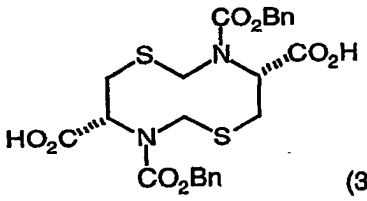
Scheme 13

During the studies to solve the cysteine manipulation problems, the use of the cystine carbamate (35) (Scheme 14) was also trialed. Oxazolidinone formation gave the dimeric structure (36) as a solid (33%). However, the reductive cleavage resulted in isolation of the thiazolidine (30). Evidently, the disulfide bridge is cleaved initially giving the cysteine oxazolidinone (31a) *in situ*. This was then transformed into the expected iminium ion, which reacts with the thiol, as before, to give the thiazolidine (30).



Scheme 14

In addition, it was reported[27] the oxazolidination of cysteine led to the formation of the dimeric structure (37). In reality this dimeric structure is a proton sharing aggregate of two thiazolidines (30) that forms in the conditions of the e.s.m.s. The proposal of the structure (37) was based on the observance in the electrospray mass spectrum of *m/z* 535 corresponding to the M+H ion of the aggregate of the monomer (30). However, further analysis of the cysteine product revealed the appearance of the *m/z* 535 peak was concentration dependent. Furthermore, while the e.s.m.s. of the putative aggregate also exhibited peaks at *m/z* 557 and 268 corresponding to M+Na and M+2/2, that same spectrum did not show a peak at *m/z* 279 for M+Na+H/2. The *m/z* 268 peak is revealed as the M+H ion for the thiazolidine (30). Thus, the dimer (37) is not formed in the cysteine oxazolidination; only the thiazolidine (30) is formed in that reaction.



(37)

(R)-3-Benzyloxycarbonyl-4-(acetylthiomethyl)oxazolidin-5-one (32)

In a round-bottomed flask fitted with a Dean-Stark apparatus, a mixture of the *S*-acetyl cysteine (31b) (1.0 g, 3.4 mmol), paraformaldehyde (450 mg) and camphorsulfonic acid (40 mg) was suspended in benzene (30 ml). The mixture was heated to reflux for 3 h (monitored by TLC). The reaction mixture was then concentrated at reduced pressure. The residue was taken up in ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution to remove acidic material. The organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by column chromatography, eluting with 50% ethyl

acetate-hexane to afford the oxazolidinone (32) as an oil (540 mg, 51%) (Found: C, 54.47; H, 4.94; N, 4.32; S, 10.29. $C_{14}H_{15}NO_5S$ requires C, 54.36; H, 4.89; N, 4.53; S, 10.37%). $[\alpha]_D^{25}$ +101.0° (*c*, 0.9 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3110, 3090, 3065 and 3034 (CH, aromatic), 3000-2800 (CH, saturated), 1804 (C=O, oxazolidinone), 1714 (C=O, carbamate, acetate), 1500, 1412, 1357, 1290, 1215, 1168, 1129, 1051, 1020, 966, 884, 764, 699, 620. δ_H 7.35-7.30, m, 5H, ArH; 5.44, bs, 1H, NCHHO; 5.22-5.14, m, 3H, $ArCH_2$ and NCHHO; 4.52, bs, 1H, NCHCO; 3.65, dd, *J* 4.7 and 14.2 Hz, 1H, CHHS; 3.41-3.30, m, 1H, CHHS; 2.29, s, 3H, $COCH_3$. δ_C 193.03 SCO; 170.28, C5; 152.39, OCON; 135.17, quaternary ArC; 128.51, 128.45, 128.24 and 127.82, ArC; 78.39, NCH_2O; 68.03, $ArCH_2$; 54.60, C4; 30.36, CH_3; 29.36, CH_2S.

(R)-3-Benzyloxycarbonyl-4-(phenylmethylthiomethyl)oxazolidin-5-one (33)

In a round-bottomed flask fitted with a Dean-Stark apparatus, a mixture of the *S*-benzyl cysteine (31c) (1.0 g, 2.9 mmol), paraformaldehyde (450 mg) and camphorsulfonic acid (50 mg) was suspended in benzene (30 ml). The mixture was heated to reflux (monitored by TLC for disappearance of starting material). The reaction mixture was then concentrated at reduced pressure. The residue was taken up in ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution to remove acidic material. The organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The pale yellow syrupy residue was purified by column chromatography, eluting with 20% ether-hexane then 20-50% ethyl acetate-hexane to afford the oxazolidinone (33) as a clear colourless oil (920 mg, 89%) (Found: C, 63.59; H, 5.62; N, 4.07. $C_{19}H_{19}NO_4S$ requires C, 63.85; H, 5.36; N, 3.92%). $[\alpha]_D^{24}$ +102.3° (*c*, 0.6 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3086, 3062, 3030 and 3006 (CH, aromatic), 3000-2800 (CH, saturated), 1801 (C=O, oxazolidinone), 1717 (C=O, carbamate), 1495, 1452, 1413, 1357, 1290, 1257, 1212,

1165, 1127, 1052, 1019, 961, 764, 699. δ_H 7.34-7.20, m, 10H, ArH; 5.50, bs, 1H, NCHHO; 5.35, d, *J* 4.1 Hz, 1H, NCHHO; 5.16, s, 2H, $ArCH_2O$; 4.50, bs, 1H, NCHCO; 3.69, d, J_{AB} 13.3 Hz, 1H, ArCHHS; 3.65, d, J_{AB} 13.3 Hz, 1H, ArCHHS; 3.37-2.89, m, 2H, $CHCH_2S$. δ_C 171.28, C5; 152.38, OCON; 137.45, 135.23, quaternary ArC; 128.95, 128.69, 128.55, 128.32 and 127.28, ArC; 78.77, C2; 68.01, $ArCH_2O$; 56.05, C4; 37.24, $ArCH_2S$; 31.90 and 31.40, $CHCH_2S$.

N-Benzyloxycarbonyl-N-methyl-S-phenylmethyl-L-cysteine (34)[56]

The oxazolidinone (33) (850 mg, 2.4 mmol) was taken up in chloroform (20 ml). Triethylsilane (1.5 ml) was added followed by trifluoroacetic acid (20 ml) and the resulting mixture was left to stand for 2 d. The reaction mixture was concentrated under reduced pressure. The residue was diluted with excess saturated aqueous sodium bicarbonate solution. The aqueous phase was washed with ether and then acidified to pH 2 with 2 M hydrochloric acid. The acidic layer was then extracted with ether. The ethereal extracts were dried ($MgSO_4$) and then treated with dicyclohexylamine (2.4 mmol) and the solution was stored overnight at 0°C. The crystalline precipitate that formed was filtered off at the pump and dried to give the *N*-methyl-*S*-benzyl cysteine (31) as its DCHA salt (900 mg, 70%) m.p. 105-107°C (Found: C, 68.91; H, 8.39; N, 5.05; S, 5.85. $C_{31}H_{44}N_2O_4S$ requires C, 68.85; H, 8.20; N, 5.18; S, 5.93%). $[\alpha]_D^{26}$ -56.0° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr disk) 3059 and 3029 (CH, aromatic), 3000-2800 (CH, saturated), 2525 and 2466 (H_2N^+), 1692 (C=O, carbamate), 1624 (CO_2^-), 1563, 1496, 1476, 1453, 1382, 1311, 1293, 1169, 1128, 1024, 760, 700. δ_H (rotamers) 7.35-7.17, m, 10H, ArH; 5.25-5.03, m, 2H, $ArCH_2O$; 4.76, dd, *J* 4.9 and 10.6 Hz, 1H, NCHCO; 4.61, dd, *J* 4.9 and 10.5 Hz, 1H, NCHCO; 3.73-3.61, m, 2H, $ArCH_2S$; 3.12-3.05, m, 1H, CHCHHS; 2.89-2.83, m, 5H, NCH_3 and CHNCH; 2.71-2.65, m, 1H, CHCHHS; 1.91-1.03, m, 20H, 10 x CH_2. δ_C (rotamers) 173.99 and 173.66, C=O; 157.07

and 156.78, OCON; 138.49, 137.04 and 136.85, 2 x quaternary ArC; 128.92, 128.73, 128.27, 127.70, 127.46 and 126.69, 10 x ArC; 67.04 and 66.83, $ArCH_2O$; 60.31 and 59.79, 2 x CHNCH; 52.37, NCHCO; 36.17 and 35.76, $ArCH_2S$; 32.21 and 31.75, $CHCH_2S$; 30.62 and 30.29, NCH_3; 28.93, 28.81, 25.11 and 24.67, 10 x CH_2.

(4R,4'R)-3,3'-Bis-benzyloxycarbonyl-4,4'-[dithiobis(methylene)]bis-oxazolidin-5-one (36)

A mixture of the cystine carbamate (35) (3.0 g, 5.9 mmol), camphorsulfonic acid (40 mg), paraformaldehyde (2.0 g) and toluene (100 ml) was heated to reflux (*ca.* 1.5 h, TLC). The reaction mixture was then concentrated under reduced pressure and the residue was filtered through a short column or plug of silica gel eluting with dichloromethane. The filtrate was concentrated *in vacuo* and the residual syrup was refrigerated at ~5°C overnight to initiate crystallisation. The mixture of syrup and most of the solid was taken up in hot ether solution (small amounts of ethyl acetate can be added to facilitate dissolution). The solution was concentrated by boiling to *ca.* 15 ml and then hexane (10 ml) was added. The solution was left to stand overnight at 0°C. The precipitate that formed was filtered off at the pump and dried to give the oxazolidinone (36) as a crystalline solid (1.05 g, 33%), m.p. 86-88 °C (Found: C, 54.11; H, 4.46; N, 5.17; S, 11.96. $C_{24}H_{24}N_2O_8S_2$ requires C, 54.12; H, 4.54; N, 5.26; S, 12.04%). $[\alpha]_D^{23}$ +99.4° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr disk) 3090, 3065, and 3033 (CH, aromatic), 3000-2800 (CH, saturated), 1796 (C=O, oxazolidinone), 1704 (C=O, carbamate), 1500, 1453, 1431, 1362, 1296, 1268, 1213, 1175, 1159, 1125, 1055, 761, 700. δ_H 7.34-7.29, m, 10H, ArH; 5.49-5.46, m, 2H, 2 x NCHHO; 5.30, bs, 2H, 2 x NCHHO; 5.15-5.12, m, 4H, 2 x $ArCH_2$; 4.51, bs, 2H, 2 x NCHCO; 3.47-3.12, m, 4H, 2 x $CHCH_2S$. δ_C 170.62, C5, C5'; 152.15, 2 x OCON; 135.19, 2 x quaternary ArC; 128.66 and 128.42, 10 x

ArC; 78.43, C2, C2'; 68.04, 2 x $ArCH_2O$; 55.07, C4, C4'; 38.86 and 37.85, 2 x CH_2S.

Attempted Reductive Cleavage of the Cystine Oxazolidinone (36)

The cystine oxazolidinone (36) (300 mg, 0.6 mmol) was taken up in chloroform (5 ml). Triethylsilane (750 µl) was added followed by trifluoroacetic acid (5 ml) and the reaction mixture was left to stand for 2 d. Work-up of the reaction mixture as described for the *N*-methyl cysteine (33) afforded the thiazolidine (30) as an oil (241 mg, 80%) identical in all respects to material previously reported.[28,56]

Example 3 Methionine

The methionine carbamate reacts well to form the oxazolidinone (28b) (Figure 3), but the reductive cleavage was not successful and gave a mixture of products. This was attributed to the sidechain thioether acting as a cation scavenger (Figure 4); a phenomenon, which is known in peptide chemistry through the use of dimethyl sulfide.[41]

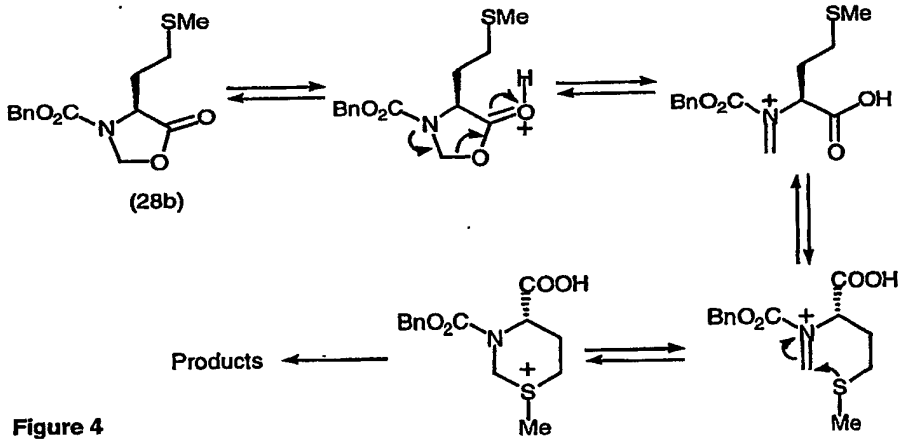
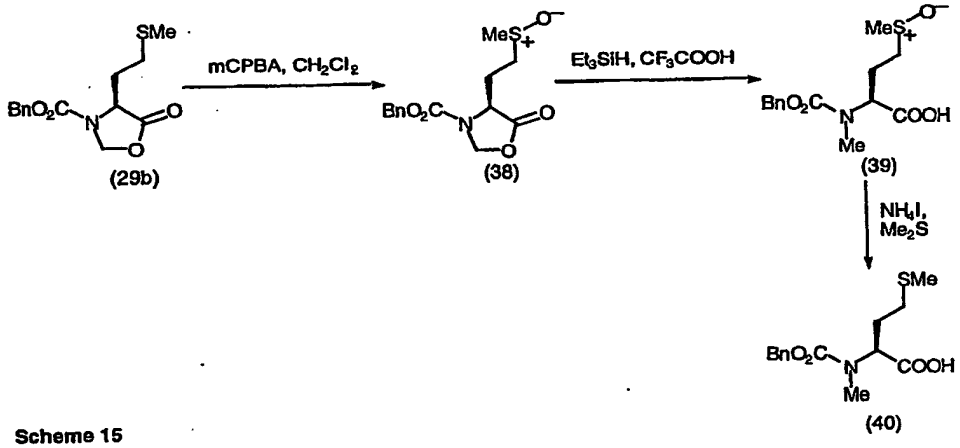


Figure 4

As with cysteine, the nucleophilicity of the thiomethyl group needed to be ameliorated to prevent its participation in the reductive cleavage. The

corresponding sulfoxide (35)[42] (95%) was easily prepared (Scheme 15) by reaction of the oxazolidinone (29b) with *meta*-chloroperoxybenzoic acid (mCPBA). Initial attempts to convert the methionine carbamate (28b) to its sulfoxide[43] were successful but the subsequent oxazolidination was compromised by the poor solubility of the sulfoxide. The sulfoxide (28) was then reductively cleaved in high yield (85%) to give the *N*-methyl amino acid (39). Treatment of this with ammonium iodide in the presence of dimethyl sulfide effects a deoxygenation giving *N*-methyl methionine as its carbamate (40) (81%).[44]



Scheme 15

(S)-3-Carbonylbenzyloxy-4-(2-methanesulfinylethyl)-oxazolidin-5-one (38)[42]

To a solution of the methionine oxazolidinone (29b) (3.0 g, 10.2 mmol) in dichloromethane (135 ml) was slowly added 3-chloroperoxybenzoic acid (1.74 g) and the reaction mixture was stirred at room temperature for 15 min. The solution was washed with sodium carbonate solution (3 x 40 ml, 10% w/v). The aqueous washings were extracted with dichloromethane (2 x 50 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the sulfoxide (35) as a clear colourless gum (3.1 g, 98%). This material was sufficiently pure to be used directly in the next step. A sample was further purified by column chromatography eluting with chloroform to afford a diastereoisomeric

mixture of the sulfoxides (38) as a colourless gum (Found: M^+, 311.0832. Calc. for $C_{14}H_{17}NO_5S$: M^+, 311.0827). ν_{max}/cm^{-1} (NaCl) 3038 (CH, aromatic), 3000-2900 (CH, saturated), 1796 (C=O, oxazolidinone), 1714 (C=O, carbamate), 1502, 1413, 1356, 1317, 1247, 1132, 1049, 753. δ_H 7.32, s, 5H, ArH; 5.48-5.47, m, 1H, NCHHO; 5.22-5.08, m, 3H, NCHHO and $ArCH_2$; 4.38, t, *J* 6.0 Hz, 1H, H4; 2.75, brs, 2H, CH_2S; 2.47, s, 3H, SCH_3; 2.38-2.27, m, 2H, $CHCH_2$. δ_C 171.09, C5; 152.89 and 152.83, OCON; 135.00, quaternary ArC; 128.61 and 128.33, ArC; 77.74, C2; 68.13, $ArCH_2$; 53.79 and 53.68, C4; 49.28, CH_2S; 38.54 and 38.47, SCH_3; 24.39 and 24.08, $CHCH_2$.

N-Benzyloxycarbonyl-N-methyl-L-methionine-d-sulfoxide (39a) and N-Benzyloxycarbonyl-N-methyl-L-methionine-l-sulfoxide (39b)

To a solution of the sulfoxides (38) (1.3 g, 4.2 mmol) in chloroform (22 ml) was added triethylsilane (2.0 ml) and trifluoroacetic acid (22 ml). The reaction mixture was stirred at room temperature for 2 d and it was then concentrated at reduced pressure. The residue was taken up in ethyl acetate and extracted with sodium carbonate solution (10% w/v, 4 x 15 ml). The combined aqueous extracts were washed with ethyl acetate and then acidified with 5 M hydrochloric acid. The aqueous layer was then extracted with dichloromethane (3 x 20 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue (1.22 g) was taken up in methanol (12 ml). To the methanolic solution was added concentrated hydrochloric acid (20 µl). 30% Hydrogen peroxide was added dropwise until TLC indicated the presence of a single compound. The reaction mixture was concentrated at reduced pressure and the residue was taken up in dichloromethane and washed with water. The dichloromethane phase was then dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue (1.22 g) was recrystallised from ethyl acetate-ether to give the

sulfoxide (39a) as a solid (210 mg, 16%), m.p. 145-148° (Found, C, 53.56; H, 6.25; N, 4.39; S, 10.35. $C_{14}H_{19}NO_5S$ requires C, 53.66; H, 6.11; N, 4.47; S, 10.23%). $[\alpha]_D^{25}$ +21.0° (*c*, 1.0 in MeOH). ν_{max}/cm^{-1} (KBr) 3600-3200 (CO_2H), 3063 and 3031 (CH, aromatic), 3000-2800 (CH, saturated), 1721 (CO, acid), 1691 (CO, carbamate), 1629, 1492, 1456, 1407, 1366, 1303, 1222, 1146, 987. δ_H (rotamers) [(D_6)dimethylsulfoxide) 7.39-7.28, m, 5H, ArH; 5.10-5.02, m, 2H, $ArCH_2$; 4.60-4.53, m, 1H, NCHCO; 2.82-2.70, m, 3H, NCH_3; 2.67-2.58, m, 2H, CH_2S; 2.51-2.47, m, 3H, SCH_3; 2.22-2.20, m, 1H, NCHC**H**H; 2.06-1.97, m, 1H, NCHCH**H**; δ_C (rotamers) 171.81 (COOH), 156.08 and 155.59 (OCON); 136.72 (quaternary ArC), 128.43, 128.36, 127.84, 127.38 (5 x ArC), 66.48 ($ArCH_2$), 58.44 (N**C**HCO), 49.99 (CH_2S), 38.11 (SCH_3), 31.86 and 31.30 (NCH_3), 22.18 and 21.50 (NCH**C**H_2). The mother liquor was concentrated at reduced pressure to afford the sulfoxide (36b) as a colourless gum (1.00 g, 76%) (Found: M^+, 314.1074. $C_{14}H_{19}NO_5S$ requires M^+, 314.1062). $[\alpha]_D^{25}$ -53.2° (*c*, 1.0 in MeOH). ν_{max}/cm^{-1} (NaCl) 3500-3200 (COOH), 3063 and 3023 (CH, aromatic), 3000-2800 (CH, saturated), 1700 (CO, acid), 1550, 1455, 1404, 1317, 1222, 1169, 1132, 1001, 823, 742, 693. δ_H (rotamers) [(D_6)dimethylsulfoxide) 7.37-7.29, m, 5H, ArH; 5.10-5.03, m, 2H, $ArCH_2$; 4.63-4.56, m, 1H, NCHCO; 2.83-2.70, m, 4H, NCH_3 and C**H**HS; 2.59-2.49, m, 4H, SCH_3 and CH**H**S; 2.25-2.20, m, 1H, NCHC**H**H; 2.10-1.97, m, 1H, NCHCH**H**; δ_C (rotamers) 171.87 (COOH), 156.12 and 155.65 (OCON), 136.81 (quaternary ArC), 128.44, 128.37, 127.81, 127.38 (5 x ArC), 66.50 ($ArCH_2$), 57.94 and 57.76 (N**C**HCO), 49.68 and 49.48 (CH_2S), 37.83 (SCH_3), 31.62 and 31.15 (NCH_3), 21.54 and 21.23 (NCH**C**H_2).

N-Benzyloxycarbonyl-N-methyl-L-methionine (40)[57]

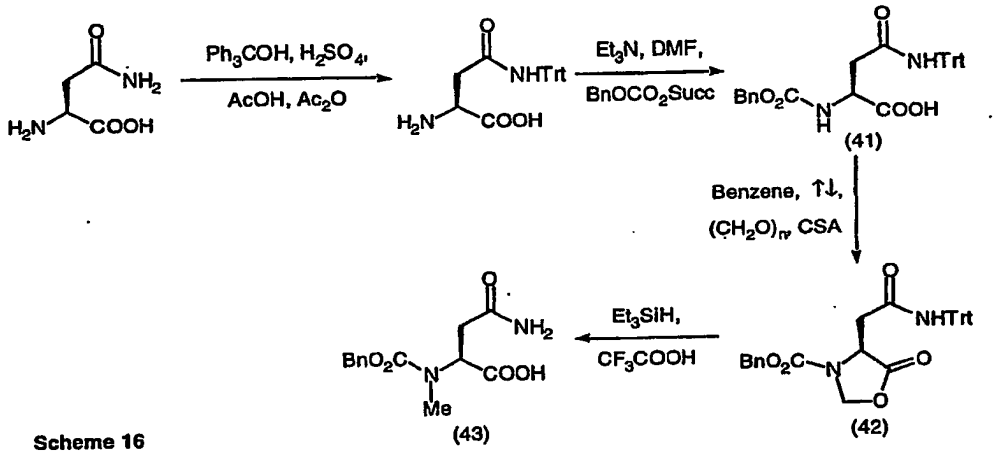
To a solution of the sulfoxides (39) (1.3 g, 4.2 mmol) in chloroform (22 ml) was added triethylsilane (2.0 ml) and trifluoroacetic acid (22 ml). The reaction mixture was stirred at room temperature for 2 d. The

solution was then cooled to 0 °C and ammonium iodide (3.02 g) and dimethylsulfide (1.53 ml) were added. The reaction mixture was stirred vigorously for 1 h at 0°C and then it was diluted with toluene and evaporated at reduced pressure. The residue was taken up in ether and extracted with sodium carbonate solution (10% w/v, 4 x 15 ml). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 5 M hydrochloric acid. The aqueous layer was then extracted with dichloromethane (3 x 20 ml) and the combined organic extracts were washed with 5% sodium thiosulfate solution, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the methionine (40) as a clear colourless oil (1.01 g, 81%). For analytical purposes this material can be taken up in ether and treated with dicyclohexylamine (1 eq.) to give the DCHA salt m.p. 97-99° (Found, C, 65.32; H, 8.54; N, 5.99. $C_{26}H_{42}N_2O_2S$ requires C, 65.24; H, 8.84; N, 5.85%). $[\alpha]_D^{23}$ -17.0° (c, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr) 3037 (CH, aromatic), 3000-2800 (CH, saturated), 2525 and 2452 (NH_2^+), 1702 (CO, carbamate), 1631 (CO_2^-), 1546, 1517, 1483, 1440, 1390, 1320, 1268, 1170, 1121, 1062, 740. δ_H (rotamers) 9.47, brs, 2H, $^+NH_2$; 7.34-7.22, m, 5H, ArH; 5.15-4.95, m, 2H, $ArCH_2$; 4.59-4.51, m, 1H, NCHCO; 2.88-2.82, m, 5H, NCH_3 and CHNCH; 2.53-2.22, m, 3H, 3 of CH_2CH_2S; 2.03 and 1.99, 2 x s, 3H, SCH_3; 1.90-1.02, m, 21H, 10 x CH_2 and 1 of CH_2CH_2S; δ_C (rotamers) 174.68 and 174.60 (COO^-), 156.83 (OCON), 136.96 and 136.83 (quaternary ArC), 128.18, 127.56, 127.38 (5 x ArC), 66.78 and 66.65 ($ArCH_2$), 60.44 and 60.16 (CHNCH), 52.29 (NCHCO); 31.56 (CH_2S), 30.54 and 30.15 (NCH_3), 29.70 and 29.66 ($NCHCH_2$), 28.94, 28.69, 25.07 and 24.61 (10 x CH_2); 15.40 (SCH_3).

Example 4 Asparagine

Carbamoylation of the sidechain of glutamine allowed its conversion to *N*-methyl glutamine.[28] This protection strategy was not possible with asparagine and

so alternatives were sought. Tritylation (Trt) of the asparagine amide sidechain was achieved under acidic conditions (Scheme 16).[45] Carbamoylation using *N*-(benzyloxycarbonyloxy)succinimide ($BnOCO_2Succ$) then gave the precursor (41)[45] for the oxazolidination and that reaction afforded the oxazolidinone (42) (83%). It should be noted the solubility of the asparagine carbamate (41) was not high and a minimal amount of DMF was included in the reaction protocol to improve substrate solubility and reaction yield. By this measure the reaction yield was increased by approximately 25-30% over the same reaction not including DMF. Reductive cleavage of the oxazolidinone (42) gave a good yield (75%) of the desired *N*-methyl product (43). The low solubility of the *N*-methyl intermediate (43) necessitated work-up by concentration of the reaction mixture and column chromatography of the residue rather than the normal aqueous procedure.



Scheme 16

(S)-3-Carbonylbenzyloxy-4-(triphenylmethylaminoacetoyl)-oxazolidin-5-one (42)

The carbamate (41) (2.54 g, 5.0 mmol) was dissolved in a minimum of DMF (*ca.* 2-3 ml). The solution was then added to toluene (120 ml), followed by camphorsulfonic acid (50 mg) and paraformaldehyde (5 g). The mixture was heated to reflux until the reaction was complete, *ca.* 2 h (monitored by TLC, 40% ethyl acetate-

hexane). The reaction mixture was concentrated under reduced pressure and the residue was taken up in ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution to remove acidic material. The organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by column chromatography, eluting with 40% ethyl acetate-hexane to afford the oxazolidinone (42) as a solid (2.16 g, 83%). A sample of the foam was recrystallised from hot ether-ethyl acetate to give a solid m.p. 122-123 °C (Found: C, 73.94; H, 5.39; N, 5.24. $C_{32}H_{28}N_2O_5$ requires C, 73.83; H, 5.42; N, 5.38%). $[\alpha]_D^{23}$ +60.3° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr disk) 3352 (CONH), 3088, 3060, 3031 and 3007 (CH, aromatic), 3000-2800 (CH, saturated), 1797 (C=O, oxazolidinone), 1710 (C=O, carbamate), 1685 (C=O, amide), 1519, 1494, 1449, 1417, 1360, 1319, 1256, 1210, 1165, 1130, 1055, 755, 721, 700. δ_H 7.36-7.04, m, 20H, ArH; 6.77 and 6.53, 2m, 1H, NH; 5.46-4.89, m, 3H, NC**H**HO and $ArCH_2$; 4.63-4.20, m, 2H, NCHCO and NCH**H**O; 3.30-2.92, m, 2H, $CHCH_2$. δ_C (rotamers) 171.68 and 167.90, 2 x C=O; 152.40, OCON; 144.03, 3 x triphenylmethyl quaternary ArC; 135.33, quaternary ArC; 128.63, 128.48, 128.27, 127.95 and 127.04, 20 x ArC; 77.83 and 77.45, NCH_2O; 70.95, CPh_3; 67.70, $ArCH_2$; 37.79 and 36.82, $CHCH_2$.

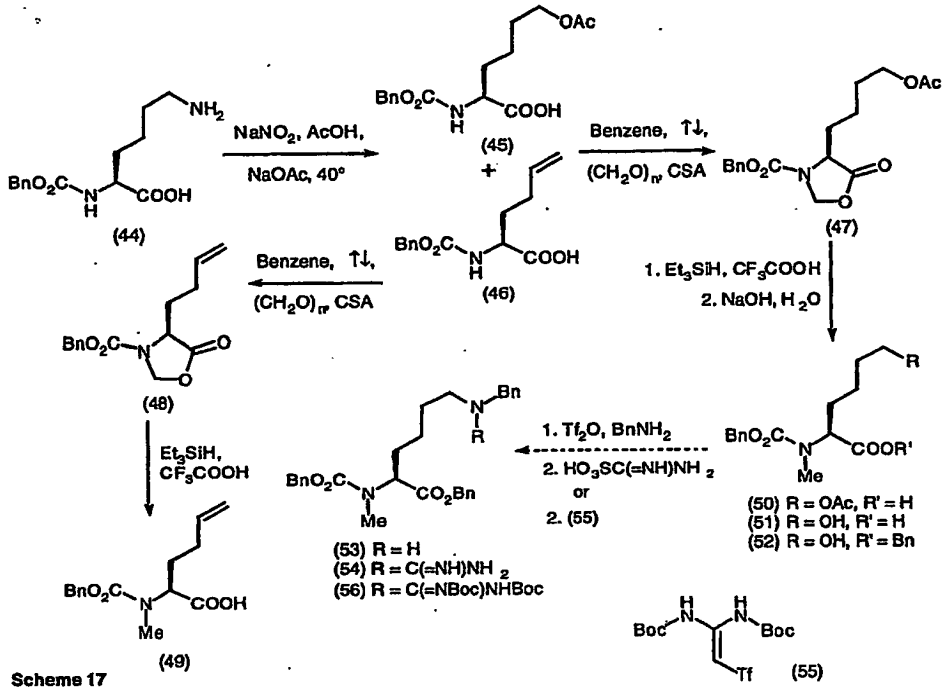
N-Benzyloxycarbonyl-N-methyl-L-asparagine (43)[58]

The oxazolidinone (42) (1.0 g, 1.9 mmol) was dissolved in chloroform (12 ml) and to this solution was added triethylsilane (1.2 ml) followed by trifluoroacetic acid (12 ml) and the reaction mixture was left to stir at room temperature for 2 d. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica eluting with 90:10:0.5 chloroform-methanol-water. The appropriate fractions were combined and concentrated under reduced pressure. The residue was triturated with ether to give the *N*-methyl asparagine (43) as a colourless solid (458 mg, 86%) m.p. 134-136°C (Found:

C, 55.65; H, 5.83; N, 9.93. $C_{13}H_{16}N_2O_5$ requires C, 55.71; H, 5.75; N, 9.99%). $[\alpha]_D^{23}$ -60.8° (*c*, 1.0 in MeOH). ν_{max}/cm^{-1} (KBr disk) 3500-3200 (CO2H), 3427 and 3219 ($CONH_2$), 3115, 3092, 3067, 3033 and 3009 (CH, aromatic), 3000-2800 (CH, saturated), 1714 (CO_2H), 1679 (C=O, carbamate), 1590, 1484, 1451, 1403, 1370, 1340, 1256, 1228, 1201, 1169, 1011, 773, 739. δ_H (d_4-MeOH) 7.34-7.25, m, 5H, ArH; 5.11, s, 2H, $ArCH_2$; 4.89-4.82, m, 1H, NCHCO; 2.97-2.89, m, 4H, NCH_3 and CHCHH; 2.79-2.66, m, 1H, CHCH**H**. δ_C (rotamers) 175.33 and 175.11 and 173.66, 2 x C=O; 158.09, OCON; 137.96 and 137.76, quaternary ArC; 129.52, 129.05, 128.98 and 128.68, 5 x ArC; 68.68 and 68.45, $ArCH_2$; 59.11 and 58.53, NCHCO; 36.79 and 36.29, $CHCH_2$; 34.05 and 33.95, NCH_3.

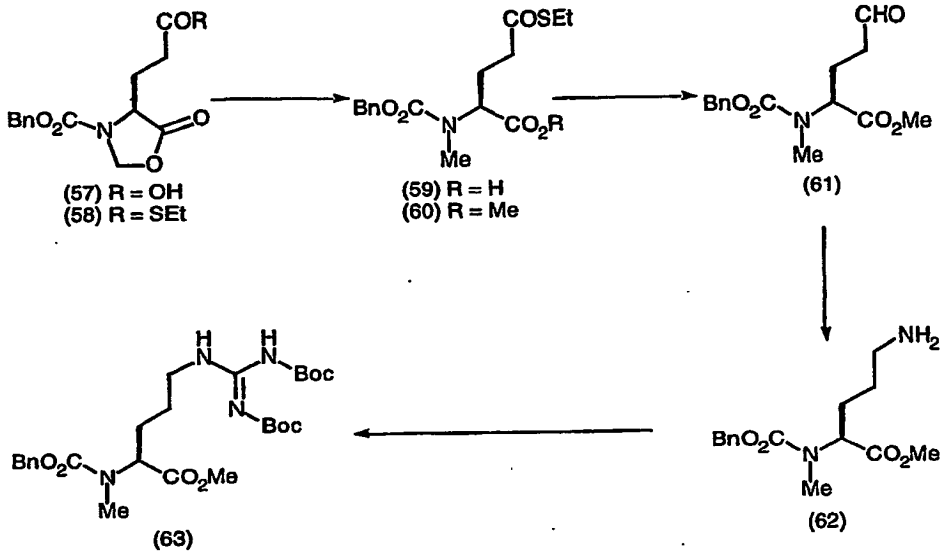
Example 5 Arginine and Homoarginine

The guanidine group of arginine presents several problems for the oxazolidinone chemistry. But *N*-methyl arginine is an attractive target given the key role arginine plays in many enzymic transformations. The lysine carbamate (44) was readily available and so the sequence in Scheme 17 leading to the *N*-methyl-lysine (53) was investigated as a trial for the preparation of *N*-methyl homoarginine. Diazotisation of the carbamate (44) and its decomposition using sodium acetate led to the formation of the acetate (45) as a mixture with the elimination product (46). These compounds were not separated prior to oxazolidination. Oxazolidination of the mixture gave the expected oxazolidinones (47) and (48), which were separated by column chromatography.



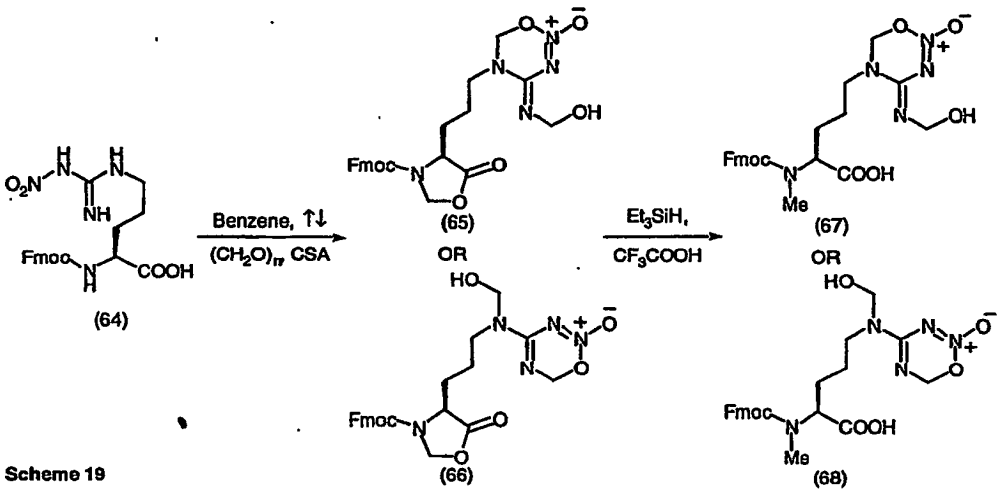
Scheme 17

Reductive cleavage of the butenyl oxazolidinone (48) gave the expected *N*-methyl amino acid (49) (64%). Reductive cleavage of the oxazolidinone (47) afforded the *N*-methyl compound (50) (82%). Then the acetate group was hydrolysed with aqueous base to give the alcohol (51) and the carboxylic acid was esterified to give the benzyl ester (52). Treatment of the benzyl ester (52) with triflic anhydride formed the triflate ester *in situ*. Benzyl amine was added to the triflate and displacement provided the fully protected *N*-methyl lysine (53). The secondary amine (53) was then treated with aminoiminomethanesulfonic acid[46] but this failed to afford the *N*-methyl homoarginine (54). In addition, reaction with the triflylguanidine (55)[47] also failed to give the desired homoarginine (56). It was evident the secondary amine was insufficiently nucleophilic for these guanylation reactions. A similar sequence with ornithine intermediates also failed for the same reasons.



Scheme 18

Scheme 18 offered a synthesis of *N*-methyl arginine *via* direct and less demanding transformations. The glutamic oxazolidinone (57) was converted to the thioester (58) (92%) by DCC coupling with ethanethiol. Reductive cleavage then proceeded smoothly to give the *N*-methyl amino acid (59) (87%). The carboxylic acid was protected as the methyl ester (60) *via* diazomethylation[48] in quantitative yield. The resulting thioester was converted into the aldehyde (66) by treatment with palladium catalyst in the presence of triethylsilane.[49] This material was not purified but was submitted directly to the next series of reactions for generating the target arginine. Reductive amination with ammonium acetate then afforded the *N*-methyl ornithine (62. Reaction of this with the guanylating reagent (55) gave the desired *N*-methyl arginine (63) in 49% yield from the methyl ester (60).



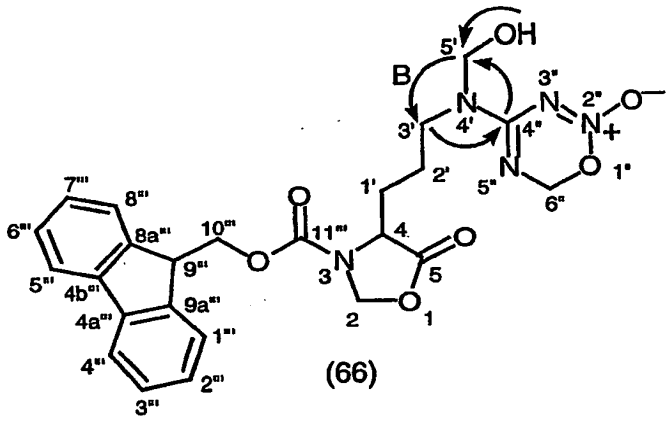
Scheme 19

In addition, conversion of the commercial Fmoc L-nitroarginine (64) was attempted. The oxazolidination reaction did not give the expected compound. Electrospray mass spectrometry and NMR analysis indicated the product had a molecular weight of 495, which required the presence of extra methylene groups. It is proposed one of the novel heterocycles (65) or (66) was prepared (Scheme 19). Similar chemistry on nitroguanidino compounds in which there is a second nucleophilic reagent, a primary amine, included in the reaction results in intermolecular condensation of the guanidine, the amine and two equivalents of the formaldehyde.[50] In the current reaction there is no second nucleophilic reactant and so, presumably, the weakly nucleophilic nitro group is able to intercept a reactive iminium intermediate and form the isolated product.

There are potentially two possible routes that the reaction can take; either to produce initially (65) or (66) and then (67) or (68). It was shown that the reaction proceeded via (66) from the detailed analysis of the NMR spectra and comparison with the data expected for structure (65). Initially the NMR spectra of compound (65) were run in $CDCl_3$, however broad peaks in both the ^1H and the ^{13}C NMR spectra were seen as a result of conformational mobility. Thus, in this solvent there were a number of

missing peaks in the 2D spectra. In DMSO at 333K it was shown that the peaks were sharper and provided satisfactory 2D spectra.

Structure (66) was identified as the reaction product and distinguished from (65) using the expected long range C-H correlations as seen in an HMBC experiment. These correlations are shown in Figure 5.



(66)

Figure 5 HMBC correlations for compound (66).

In particular, use was made of the long range C-H correlations between the protons of the hydroxymethyl group (H5') and the γ carbon of the propyl group (C3') (marked as B in Figure 2). This correlation is not possible in structure (65).

Analysis of the HMBC spectrum required an accurate assignment of all the protons and carbons in the molecule. These assignments were obtained using a combination of COSY, DEPT, HSQC and the HMBC experiments. The complete assignment is presented in Table 1.

Carbon	Carbon Shift	Proton Shift	Number of Protons	Multiplicity	J coupling
*2	77.34	5.30, 5.22	2	dd	19.95, 4.06
4	53.98	4.05	1H	t	6.3
5	171.95				
1'	26.69	1.58-1.39	2H	m	
2'	22.17	1.58-1.39	2H	m	
3'	44.79	3.24-3.18	2H	m	
5'	77.34	4.84	2H	s	
4"	153.84				
*6"	72.99	4.90-4.89	2	d	1.2
1"' (8"')	126.85	7.63-7.61	2H	d	7.13
2"' (7"')	124.59	7.31	2H	t	7.34
3"' (6"')	119.73	7.39	2H	t	7.31
4"' (5"')	127.39	7.86-7.84	2H	d	7.42
4a"' (4b"')	143.41				
8a"' (9a"')	140.62				
9"'	46.49	4.28	1H	t	5.6
10"'	66.57	4.54	2H	m	
11"'	152.44				
OH		9.6	1	s	
*Overlapping signals					

Table 1 ^{13}C and ^{1}H NMR data of compound (66) at 300 MHz, 333°K in DMSO.

The HMBC experimental data was critical in differentiating between structures (65) and (67). In both structures (65) and (66) long-range correlations from the (C4") at δ153.84 to the protons of (H3') (δ3.24-3.18), (H5') (δ4.84) and (H6") (δ4.90-4.89) would be seen. The structural difference was determined from the long-range correlation between the (C3') at (δ44.79) and the (H5') at δ4.48 of the γ-position of the propyl chain and the hydroxymethyl group. This is not possible in structure (65).

The conclusion depends upon the accurate assignment of the carbons and protons for the 1', 2' and 3' positions. Proton assignments for these positions were obtained from the mCOSY experiment, and HSQC and HMBC experiments were used for the carbon assignments.

The reductive cleavage produces a single product that has a molecular weight of 467 (e.s.m.s.). The ^{1}H and ^{13}C NMR spectra clearly indicate the presence of the *N*-methyl group and a methylene group associated with the oxatriazine. The reduction of the oxazolidinone (66) to the acid (68) shows the disappearance of the H2 proton peaks at δ5.35 and appearance of the expected NCH_3 at δ2.72 indicating that only the oxazolidinone ring is reductively cleaved. It is apparent that the triethylsilane/trifluoroacetic acid is able to reduce the 5-oxazolidinone but not the new heterocyclic ring formed from the nitroguanidine.

Preparation of the lysine derived oxazolidinones (47) and (48)

Deamination *via* diazotisation of the lysine carbamate (44) (1.01 g, 3.1 mmol) according to the method of Hutton[59] afforded the acetate (48) and the alkene (46) as a mixture (1.0 g) which, was not purified. The crude acetate (45) was taken up in benzene (30 ml) and camphorsulfonic acid (35 mg) and paraformaldehyde (3 g) were added. The mixture was heated to reflux for 2 h and then allowed to cool. The mixture was concentrated at reduced pressure and the residue was taken up in ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution to remove acidic material. The organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by column chromatography, eluting with 30% ethyl acetate-hexane to afford firstly, the oxazolidinone (46) as a clear colourless oil (113 mg, 13%) (Found: C, 65.42; H, 6.31; N, 5.07. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N,

5.09%). $[\alpha]_D^{25}$ +112.6° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3076 and 3034 (CH, aromatic), 3000-2800 (CH, saturated), 1801 (C=O, oxazolidinone), 1716 (C=O, carbamate), 1506, 1413, 1357, 1316, 1251, 1164, 1128, 1050, 919, 754, 693. δ_H 7.34-7.29, m, 5H, ArH; 5.70, brs, 1H, =CH; 5.49, brs, 1H, NCHHO; 5.31-4.95, m, 5H, $ArCH_2$, NCHHO and CH_2CHCH_2; 4.31, brs, 1H, NCHCO; 2.12-1.59, m, 4H, 2 x CH_2. δ_C (rotamers) 172.10, C=O oxazolidinone; 152.68, OCON; 136.36, =CH; 135.35, quaternary ArC; 128.58, 128.50, 128.19 and 127.69, ArC; 115.79, $=CH_2$; 77.77, NCH_2O; 67.80 and 67.67, $ArCH_2$; 55.16, 54.96 and 54.24, NCHCO; 29.60 and 28.43, 2 x CH_2. Further elution gave the oxazolidinone (47) as a colourless oil (478 mg, 46%) (Found: C, 60.80; H, 6.41; N, 4.26. $C_{17}H_{21}NO_6$ requires C, 60.89; H, 6.31; N, 4.18%). $[\alpha]_D^{25}$ +86.6° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3067 and 3033 (CH, aromatic), 3000-2800 (CH, saturated), 1801 (C=O, oxazolidinone), 1724 (2 x C=O), 1506, 1413, 1361, 1318, 1244, 1167, 1131, 1047, 755, 696. δ_H 7.33, s, 5H, ArH; 5.48, brs, 1H, NCHHO; 5.23-5.09, m, 3H, $ArCH_2$ and NCHHO; 4.27, t, *J* 5.2 Hz, 1H, NCHCO; 3.97, t, *J* 6.2 Hz, 2H, CH_2OAc; 2.04-1.76, m, 2H, CH_2; 1.98, s, 3H, OAc; 1.43-1.32, m, 4H, 2 x CH_2. δ_C 172.03 and 170.80, 2 x C=O; 152.78, OCON; 135.29, quaternary ArC; 128.56, 128.49 and 128.16, ArC; 77.80, NCH_2O; 67.80, $ArCH_2$; 63.71, CH_2OAc; 54.64, NCHCO; 30.18, $CHCH_2$; 27.99, CH_2; 20.79, CH_2; 20.76, OAc.

(S)-N-Benzyloxycarbonyl-N-methyl-2-(3-butenyl)-glycine (49)

The oxazolidinone (48) (310 mg, 1.1 mmol) was taken up in chloroform (6 ml) and triethylsilane (540 µl) was added followed by trifluoroacetic acid (6 ml) and the mixture was left to stand at room temperature for 2 d. The reaction mixture was diluted with toluene and then concentrated *in vacuo* and the residue was taken up in ether and extracted with aqueous sodium carbonate solution (4 x 2 ml). The combined aqueous extracts were washed

with ether and then acidified to ~pH 2 with 5 M hydrochloric acid. The aqueous phase was then extracted with dichloromethane (3 x 5 ml). The organic phase was dried ($MgSO_4$), filtered and evaporated to give a yellow oil (230 mg). The oil was chromatographed on silica eluting with 94:5.5:0.5 chloroform-methanol-water to provide the *N*-methyl amino acid (49) as a clear colourless oil (200 mg, 64%) (Found: M+H, 278.1384. $C_{15}H_{19}NO_4$ requires M+H, 278.1392). $[\alpha]_D^{24}$ -16.6° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3600-3000 (COOH), 3077 and 3038 (CH, aromatic), 3000-2800 (CH, saturated), 1705 (C=O), 1548, 1451, 1402, 1321, 1210, 1153, 1035, 916, 854, 740, 692. δ_H (rotamers) 10.02, brs, 1H, COOH; 7.34-7.30, m, 5H, ArH; 5.86-5.50, m, 1H, =CH; 5.19-4.63, m, 5H, $ArCH_2$, $=CH_2$, and NCHCO; 2.89-2.88, m, 3H, NCH_3; 2.12-1.60, m, 4H, 2 x CH_2. δ_C (rotamers) 176.66 (COOH), 157.14 and 156.45, OCON; 136.64 and 136.47, =CH; 136.32 and 136.15, quaternary ArC; 128.39, 127.97, 127.80 and 127.68, ArC; 116.03 and 115.85, $=CH_2$; 67.61, $ArCH_2$; 58.06 and 57.80, NCHCO; 31.02 and 30.63, NCH_3; 30.10 and 29.95, CH_2; 27.96 and 27.69, CH_2.

(S)-N-Benzyloxycarbonyl-N-methyl-2-(4-acetoxybutanyl)-glycine (50)

The oxazolidinone (47) (3.26 g, 9.7 mmol) was taken up in dichloromethane (50 ml) and triethylsilane (5.0 ml) was added followed by trifluoroacetic acid (50 ml) and the mixture was left to stand at room temperature for 2 d. The reaction mixture was concentrated *in vacuo* and the residue was taken up in aqueous sodium bicarbonate solution, and washed with ether. The aqueous was then acidified 5 M hydrochloric acid and extracted with dichloromethane. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a yellow oil (2.69 g, 82%) which was used directly in the next step.

(S)-N-Benzyloxycarbonyl-N-methyl-2-(4-hydroxybutanyl)-glycine (51)

The crude acetate (50) (1.67 g, 4.9 mmol) was treated with 1 M sodium hydroxide solution (10.8 ml) at 0°C and left to stir at that temperature for 1.5 h. The solution was then acidified with dilute hydrochloric acid and extracted with chloroform (6 x 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was triturated with ether to afford the alcohol (51) as a colourless solid (1.2 g, 83%) m.p. 122-124° (Found: C, 60.87; H, 7.34; N, 4.65. $C_{15}H_{21}NO_5$ requires C, 61.00; H, 7:17; N, 4.74%). $[\alpha]_D^{24}$ -22.3° (*c*, 1.0 in acetone). ν_{max}/cm^{-1} (KBr disk) 3600-3200 (CO_2H and OH), 3095 and 3030 (CH, aromatic), 3000-2800 (CH, saturated), 1738 (C=O, acid), 1650 (C=O, carbamate), 1490, 1405, 1322, 1258, 1206, 1162, 1101, 1024, 763. δ_H [300 MHz, (D_6)acetone] (rotamers) 7.38-7.31, m, 5H, ArH; 5.14-5.12, m, 2H, $ArCH_2$; 4.76, dd, *J* 4.7 and 10.9 Hz, O.5H, NCHCO; 4.65, dd, *J* 4.7 and 10.7 Hz, 0.5H, NCHCO; 3.55, t, *J* 4.9 Hz, 2H, CH_2OH; 2.89-2.87, m, 3H, NCH_3; 1.95-1.35, m, 6H, 3 x CH_2. δ_C (rotamers) 172.99, COOH; 157.51 and 156.85, OCON; 138.06, quaternary ArC; 129.18, 128.56 and 128.34, ArC; 67.49, $ArCH_2$; 62.14, CH_2OH; 59.03, NCHCO; 32.94, CH_2; 31.05 and 30.57, NCH_3; 29.45 and 29.06, CH_2; 23.37, CH_2.

(S)-N-Benzyloxycarbonyl-N-methyl-2-(4-hydroxybutanyl)-glycine benzyl ester (52)

The acid (451) (300 mg, 1.0 mmol) was dissolved in dimethylformamide (10 ml). Anhydrous potassium carbonate (210 mg) was added and the mixture was vigorously stirred while benzyl bromide (121 µl) was added. The resulting mixture was stirred at room temperature under a nitrogen atmosphere overnight. It was then diluted with water (150 ml) and extracted with ethyl acetate (3 x 20 ml) and the combined extracts were dried ($MgSO_4$) filtered and evaporated at reduced pressure to give the benzyl ester (52) as a clear gum (334 mg, 87%). A

sample was further purified by column chromatography eluting with 30% ethyl acetate-hexane to give the pure ester (52) (Found: C, 68.28; H, 7.24; N, 3.72. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.06; N, 3.63%). $[\alpha]_D^{25}$ -23.4° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3600-3200 (OH), 3094, 3065 and 3036 (CH, aromatic), 3000-2800 (CH, saturated), 1739 (C=O, ester), 1699 (C=O, carbamate), 1456, 1401, 1320, 1257, 1212, 1151, 1069, 909, 742, 693. δ_H (rotamers) 7.32-7.24, m, 10H, ArH; 5.18-5.08, m, 4H, 2 x $ArCH_2$; 4.85, dd, *J* 4.9 and 10.8 Hz, 0.5H, NCHCO; 4.62, dd, *J* 4.9 and 10.5 Hz, 0.5H, NCHCO; 3.59-3.51, m, 2H, CH_2OH; 2.86-2.83, m, 3H, NCH_3; 2.04-1.30, m, 6H, 3 x CH_2. δ_C (rotamers) 171.34 and 171.38, COOBn; 156.99 and 156.23, OCON; 136.46, 136.33; 135.49 and 135.38, 2 x quaternary ArC; 128.45, 128.35, 128.16, 127.94, 127.79 and 127.58, ArC; 67.33 and 66.67, 2 x $ArCH_2$; 62.22, CH_2OH; 58.64 and 58.36, NCHCO; 31.85, CH_2; 30.87 and 30.21, NCH_3; 28.57, 28.18, 22.24 and 22.16, 2 x CH_2.

<u>N^{α}-*Benzyloxycarbonyl*-N^{α}-*methyl*-N^{ε}-benzyl-*L-lysine benzyl ester (53)*</u>

The alcohol (52) (740 mg, 1.9 mmol) was dissolved in dry dichloromethane (9 ml) and the solution was cooled to -50°. Triethylamine (460 µl) was added followed by trifluoromethanesulfonic anhydride (490 µl). After 15 min at -50° TLC analysis indicated complete conversion to the corresponding triflate. Benzyl amine (0.82 ml) was then added in one portion at -50° and the reaction mixture was stirred at this temperature for 30 min and then at room temperature overnight. The reaction mixture was diluted with ether (100 ml) and the organic phase was washed with water (3 x 300 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated at reduced pressure. The crude residue was purified by column chromatography eluting firstly, with 60% ethyl acetate-hexane and then 8% methanol-ethyl acetate to afford the lysine (53) as a clear oil (701 mg, 78%)

(Found: C, 73.30; H, 7.35; N, 5.99. $C_{29}H_{34}N_2O_4$ requires C, 73.39; H, 7.22; N, 5.90%). $[\alpha]_D^{25}$ -18.6° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3092, 3064 and 3033 (CH, aromatic), 3000-2800 (CH, saturated), 1740 (C=O, ester), 1702 (C=O, carbamate), 1533, 1455, 1399, 1318, 1208, 1145, 1030, 739, 693. δ_H (rotamers) 7.34-7.22, m, 15H, ArH; 5.19-5.10, m, 4H, 2 x $ArCH_2$; 4.88, dd, *J* 4.9 and 10.7 Hz, 0.5H, NCHCO; 4.64, dd, *J* 4.8 and 10.4 Hz, 0.5H, NCHCO; 3.76, brs, 2H, NCH_2Ph; 2.88-2.85, m, 3H, NCH_3; 2.61, brs, 2H, CH_2N; 2.05-1.23, m, 7H, 3 x CH_2 and NH. δ_C (rotamers) 171.31 and 171.13, COOBn; 156.85 and 156.14, OCON; 140.04, 136.49, 136.33, 135.49 and 135.37, quaternary ArC; 128.39, 128.29, 128.21, 128.08, 127.97, 127.88, 127.81, 127.69, 127.53 and 126.77, ArC; 67.23 and 66.56, 2 x $ArCH_2$; 58.54 and 58.34, NCHCO; 53.74, NCH_2Ph; 48.80, CH_2N; 30.77 and 30.12, NCH_3; 29.23, 28.69, 28.33 and 23.68, 3 x CH_2.

(S)-3-Carbonylbenzyloxy-4-(2-ethylsulfanylcarbonyl-ethyl)-oxazolidin-5-one (58)

To a sample of the glutamic acid oxazolidinone (57) (2.0 g, 6.8 mmol) in dichoromethane (8 ml) was added ethanethiol (1.01 ml, 13.6 mmol) and dimethylaminopyridine (DMAP) (20 mg) and the solution was cooled to 0°C. Dicyclohexylcarbodiimide (DCC) (1.69 g, 8.2 mmol) was added in one portion and the reaction mixture was stirred at 0°C for 30 min. Acetic acid (0.8 ml) was then added and stirring was continued for 10 min. The mixture was diluted with ether (50 ml) and suction filtered. The filtrate was washed sequentially with 10% sodium carbonate solution (2 x 20 ml), water, 0.5M hydrochloric acid (20 ml), water and brine. The ethereal solution was then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the thioester (58) as an oil (2.13 g, 92%). A sample was further purified for analytical purposes by column chromatography on silica eluting with 50% ether-hexane, (Found: C, 56.72; H, 5.57; N, 4.30. $C_{16}H_{19}NO_5S$ requires C, 56.96; H, 5.68; N, 4.15%). $[\alpha]_D^{25}$ +99.2° (*c*, 1.0 in $CHCl_3$).

ν_{max}/cm^{-1} (NaCl) 3097, 3063 and 3033 (CH, aromatic), 3000-2800 (CH, saturated), 1800 (C=O, oxazolidinone), 1718 (C=O, carbamate and thioester), 1500, 1412, 1356, 1317, 1252, 1169, 1131, 1052, 998, 840, 756, 696. δ_H 7.30, s, 5H, ArH; 5.42, brs, 1H, NCHHO; 5.14, d, *J* 4.5 Hz, 1H, NCHHO; 5.12, s, 2H, $ArCH_2$; 4.27, t, 1H, *J* 5.7 Hz, NCHCO; 2.79, q, *J* 7.4 Hz, 2H, SCH_2; 2.65-2.49 and 2.36-2.11, 2m, 4H, 2 x CH_2; 1.16, t, *J* 7.4 Hz, 3H, SCH_2CH_3. δ_C 197.34, COS; 171.36, C=O oxazolidinone; 152.64, OCON; 135.12, quaternary ArC; 128.39, 128.29 and 128.04, ArC; 77.59, NCH_2O; 67.72, $ArCH_2$; 53.71, NCHCO; 38.49, SCH_2; 25.95 and 23.10, 2 x CH_2; 14.44, SCH_2CH_3.

(S)-2-(Benzyloxycarbonyl-methyl-amino)-4-ethylsulfanylcarbonyl-butyric acid (59)

A sample of the oxazolidinone (58) (1.0 g, 0.3 mmol) was dissolved in dichloromethane (15 ml) and triethylsilane (1.4 ml) was added followed by trifluoroacetic acid (15 ml) and the mixture was left to stand for 3 d at room temperature. The solution was then taken up in toluene (50 ml) and evaporated to dryness under reduced pressure. The residue was then taken up in ether and extracted with 10% sodium carbonate solution. The aqueous layer was washed with ether and then acidified to ~pH 2 with 5M hydrochloric acid. The aqueous phase was then extracted with dichloromethane (4 x 20 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residual oil (920 mg) slowly crystallised. The oil was recrystallised from ether-hexane to afford the carboxylic acid (59) as a colourless solid (880 mg, 87%) m.p. 94-96°C. (Found: C, 56.75; H, 6.30; N, 4.29. $C_{16}H_{21}NO_5S$ requires C, 56.62; H, 6.24; N, 4.13%). $[\alpha]_D^{24}$ -15.6° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr disk) 3700-3200 (CO_2H), 3134, 3097, 3069 and 3033 (CH, aromatic), 3000-2800 (CH, saturated), 1736, 1687 and 1648 (3 x C=O), 1492, 1455, 1411, 1374, 1325, 1254, 1222, 1174, 1096, 1069, 1017, 989, 767, 739. δ_H 10.22, brs, 1H, COOH;

7.32-7.27, m, 5H, ArH; 5.14, s, 2H, $ArCH_2$; 4.85-4.56, m, 1H, NCHCO; 2.88-2.81, m, 5H, NCH_3 and SCH_2; 2.65-2.05, m, 4H, 2 x CH_2; 1.21, t, *J* 7.4 Hz, 3H, SCH_2CH_3. δ_C (rotamers) 198.17, COS; 175.29, COOH; 157.11 and 156.27, OCON; 136.36, quaternary ArC; 128.50, 128.08 and 127.83, ArC; 67.84, $ArCH_2$; 58.46, NCHCO; 40.31, SCH_2; 31.47, NCH_3; 24.49 and 23.37, 2 x CH_2; 14.57, SCH_2CH_3.

(S)-2-(Benzyloxycarbonyl-methyl-amino)-4-ethylsulfanylcarbonyl-butyric acid methyl ester (60)

The title compound (60) was prepared by diazomethylation of the carboxylic acid (59) by the standard method.[48] The methyl ester (60) was isolated in 100% yield. (Found: C, 58.05; H, 6.74; N, 4.15. $C_{17}H_{23}NO_5S$ requires C, 57.77; H, 6.56; N, 3.96%). $[\alpha]_D^{24}$ -21.8° (*c*, 2.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3095, 3063 and 3029 (CH, aromatic), 3000-2800 (CH, saturated), 1743 and 1700 (3 x C=O), 1448, 1403, 1316, 1219, 1180, 1141, 1057, 1007, 907, 742, 695. δ_H (rotamers) 7.26-7.17, m, 5H, ArH; 5.06-5.04, m, 2H, $ArCH_2$; 4.67 and 4.49, 2dd, *J* 5.0 and 10.5 Hz, 1H, NCHCO; 3.59-3.52, m, 3H, OCH; 2.77-2.71, m, 5H, NCH_3 and SCH_2; 2.58-2.40 and 2.31-1.91, 2m, 4H, 2 x CH_2; 1.12, t, *J* 7.4 Hz, 3H, SCH_2CH_3. δ_C (rotamers) 197.68, COS; 170.71 and 170.59, COOMe; 156.42 and 155.65, OCON; 136.18 and 136.03, quaternary ArC; 128.08, 127.63, 127.49 and 127.34, ArC; 67.09, $ArCH_2$; 57.90, NCHCO; 51.79, OCH_3; 39.96 and 39.68, SCH_2; 31.32 and 30.57, NCH_3; 24.29, 23.99 and 22.92, 2 x CH_2; 14.34, SCH_2CH_3.

(S)-2-(Benzyloxycarbonyl-methyl-amino)-5-[tert-butoxycarbonylamino-(tert-butoxycarbonylimino)methyl]-pentanoic acid methyl ester (63)

To a sample of the thioester (60) (200 mg, 0.56 mmol) in acetone (1.0 ml) was added triethylsilane (300 µl) followed by 10% Palladium-on-charcoal catalyst (50 mg) and the reaction mixture was stirred vigorously for 1 h. The mixture was filtered through celite and the

filtrate was concentrated under reduced pressure. The residue aldehyde (61) was purified by chromatography on a short silica column eluting with 20% ethyl acetate-hexane to remove the triethylsilane. The fractions collected were concentrated *in vacuo* and the residue was taken up in methanol (4 ml) and ammonium acetate (222 mg) was added followed by sodium cyanoborohydride (71 mg) and the mixture was stirred at room temperature for 30 min. The solution was concentrated at reduced pressure to about 1 ml and it was then diluted with saturated aqueous sodium bicarbonate solution (10 ml). The aqueous phase was then extracted with dichloromethane (3 x 5 ml). The combined extracts were dried (MgSO4), filtered and concentrated *in vacuo* to give the primary amine (62). The amine (62) was taken up in chloroform (filtered through neutral alumina, 2 ml) and di-boc-triflylguanidine (221 mg, 0.56 mmol) was added followed by diisopropylethylamine (0.15 ml, 0.85 mmol) and the mixture was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure and the residue was purified by chromatography on silica eluting with chloroform. The material isolated was further purified by chromatography eluting with 50% ether-hexane to give the protected *N*-methyl arginine (63) as a clear colourless oil (149 mg, 49%). (Found: C, 58.32; H, 7.56; N, 10.22. $C_{26}H_{40}N_4O_8$ requires C, 58.19; H, 7.51; N, 10.44%). $[\alpha]_D^{19}$ -13.0° (*c*, 0.5 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3335 and 3290(sh), 2 x NH, 3133, 3104, 3076 and 3033 (CH, aromatic), 3000-2800 (CH, saturated), 1712 and 1633 (4 x C=O), 1574, 1446, 1411, 1364, 1327, 1238, 1229, 1141, 1053, 866, 809, 762, 746. δ_H (rotamers) 11.45, brs, 1H, NH; 8.28, brs, 1H, NH; 7.31-7.23, m, 5H, ArH; 5.12, d, J_{AB} 12.3 Hz, 1H, ArCHH; 5.07, d, J_{AB} 12.3 Hz, 1H, ArCHH; 4.76 and 4.57, 2dd, J 4.8 and 10.5 Hz, 1H, NCHCO; 3.65-3.58, m, 3H, OCH_3; 3.43-3.33, m, 2H, NCH_2; 2.82, s, 3H, NCH_3; 2.02-1.37, m, 22H, 2 x $C(CH_3)_3$ and 2 x CH_2. δ_C (rotamers) 171.53 and 171.35, COOMe; 163.30, N=CN; 156.81, 156.00 and 153.12, 3 x OCON; 136.41 and 136.31, quaternary ArC;

128.84, 128.32, 127.84 and 127.56, ArC; 82.98 and 79.07, 2 x **C**$(CH_3)_3$; 67.34, ArCH_2; 58.37 and 58.19, N**C**HCO; 51.99, OCH_3; 40.17 and 39.97, NCH_2; 31.07 and 30.26, NCH_3; 28.12 and 27.89, 2 x C$(CH_3)_3$; 26.12, 25.84 and 25.73, 2 x CH_2.

4S-4-{4-[4-Hydroxymethylimino-2-oxy-4H-(1,2,3,5)-oxatriazin-5-yl]-propyl}-oxazolidin-5-one-3-carboxylic acid 9H-fluoren-9-ylmethyl ester (66)

The nitroarginine carbamate (64) (1.0 g, 2.3 mmol) was dissolved in toluene (50 ml) in a round-bottomed flask fitted for reflux. To the solution was added camphorsulfonic acid (10 mg) and paraformaldehyde (1.5 g) and the mixture was heated to reflux for 1.5 h. The reaction mixture was cooled and the solvent was decanted from residual solid material. The solvent was concentrated *in vacuo* and the residue was purified by column chromatography eluting with 80% ethyl acetate-dichloromethane to afford the oxazolidinone (66) as a colourless foam (750 mg, 67%) %) (Found: M+H, 496.1816. Calc. for $C_{24}H_{26}N_5O_7$: M+H, 498.1842). ν_{max}/cm^{-1} (KBr disk) 3289 (OH), 3066, 3041, 3015 and 3007 (CH, aromatic), 3000-2800 (CH, saturated), 1798 (C=O, oxazolidinone), 1713 (C=O, carbamate), 1588, 1557, 1412, 1346, 1196, 1136, 1048, 940, 742, 709. $[\alpha]_D^{22}$ +117.8° (*c*, 1.0 in CH_2Cl_2). δ_H [(D6)dimethylsulfoxide, 298K] 9.76, s, 1H, OH; 7.93-7.34, m, 8H, ArH; 5.35, s, 2H, H2; 4.94-4.93, m, 4H, NCH_2ON and CH_2OH; 4.52, brs, 2H, $CHCH_2O$; 4.32, t, 1H, *J* 5.4 Hz, $CHCH_2O$; 3.57-3.44, m, 2H, NCH_2CO; 3.27, s, 1H, $NCHHCH_2$; 1.90-1.25, brs, 4H, $CHCH_2CH_2$. δ_H [(D_6)dimethylsulfoxide, 333K] 9.60, s, 1H, OH; 7.86-7.31, m, 8H, ArH; 5.26, dd, 2H, *J* 20.0 and 4.1 Hz, H2; 4.90, d, 2H, *J* 1.2 Hz, NCH_2ON; 4.84, s, 2H, CH_2OH; 4.54, m, 2H, $CHCH_2O$; 4.28, t, 1H, *J* 5.6 Hz, $CHCH_2O$; 4.04, t, *J* 6.4 Hz, H4; 3.24-3.18, m, 2H, NCH_2CH_2; 1.58-1.39, m, 4H, $CHCH_2CH_2$. δ_C [(D_6)dimethylsulfoxide, 298K] 172.45, C=O; 153.74, OCON; 152.75, NC=N; 143.67, 143.59 and 140.87, quaternary ArC;

127.73, 127.21, 124.98 and 120.14, ArC; 77.75 and 77.55, NCH_2ON and C2; 73.26, NCH_2OH; 66.82, $CHCH_2O$; 54.33, C4; 46.61, $CHCH_2O$; 44.98, CH_2CH_2N; 26.87 and 22.38, $CHCH_2CH_2$; δ_C [(D_6)dimethylsulfoxide, 333K] 171.95, 153.84, 152.44, 143.41 and 143.32, 140.62, 127.39, 126.85, 124.59, 124.56, 119.73, 77.34, 72.99, 66.57, 53.98, 46.49, 44.79, 26.69, 22.17.

2S-2-[(9H-Fluoren-9-ylmethylmethoxycarbonyl)-methyl-amino]-5-[hydroxymethyl-(2-oxy-6H-[1,2,3,5]oxatriazin-4-yl-amino-pentanoic acid (68)

The oxazolidinone (66) (100 mg, 0.2 mmol) was dissolved in dichloromethane (4 ml) and triethylsilane (0.3 ml) was added followed by trifluoroacetic acid (4 ml) and the reaction mixture was stirred under a nitrogen atmosphere overnight. The mixture was concentrated at reduced pressure. The residue was purified by column chromatography eluting with 10% methanol-dichloromethane to afford the *N*-methyl compound (68) as a colourless foam (60 mg, 60%) (Found: M+H, 498.1969. Calc. for $C_{24}H_{28}N_5O_7$: M+H, 498.5086). ν_{max}/cm^{-1} (KBr disk) 3700-2700 (COOH), 3300-3200 (=NH), 3064, 3039, 3018 and 3009 (CH, aromatic), 1739 (C=O), 1696 (C=O, carbamate), 1589, 1555, 1451, 1409, 1315, 1263, 1195, 1158, 1131, 1028, 992, 760, 741. $[\alpha]_D^{22}$ -12.9° (*c*, 1.0 in CH_2Cl_2). δ_H [(D_6)dimethylsulfoxide, 300K] 9.60, s, 1H, CH_2OH; 7.84-7.26, m, 8H, ArH; 4.90, s, 2H, NCH_2ON; 4.88, s, 2H, CH_2OH; 4.35-3.97, m, 4H, $CHCH_2$ and NCHCO; 3.30, s, 2H, NCH_2CH_2; 2.72, s, 3H, NCH_3; 1.70-1.40, m, 4H, CH_2CH_2CH. δ_C [(D_6)dimethylsulfoxide, 300K] 171.97, 155.63, 153.90, 143.64 and 143.59, 140.54; 127.30, 126.76, 124.65, 119.70, 77.41, 73.04, 66.56, 57.94, 46.62, 44.95, 30.16, 25.10, 24.05.

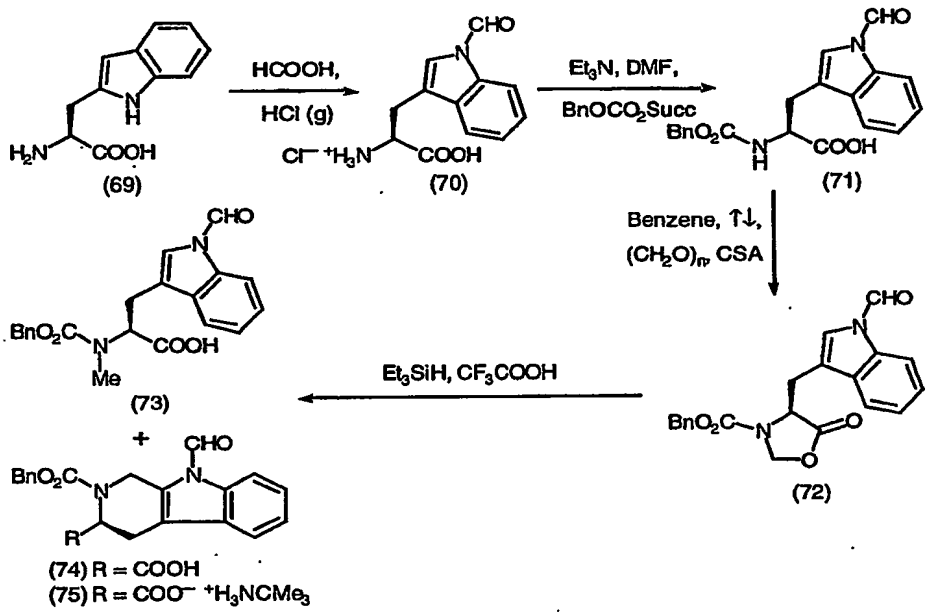
(S)-3-Carbonylbenzyloxy-4-(1-formyl-1H-indol-3-ylmethyl)-oxazolidin-5-one (72)

A mixture of the tryptophan carbamate (71) (3.0 g, 8.2 mmol), benzene (200 ml), camphorsulfonic acid (100 mg) and paraformaldehyde (5 g) was heated to reflux for 1.5 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in ether. The ethereal layer was washed with saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil. The oil was further purified by column chromatography, eluting with 60% ether-hexane to give the oxazolidinone (72) as a colourless foam (2.67 g, 86%) (Found: C, 66.87; H, 5.06; N, 7.50. $C_{21}H_{18}N_2O_5$ requires C, 66.66; H, 4.79; N, 7.40%). $[\alpha]_D^{25}$ +154.0° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr disk) 3100 and 3063 (CH, aromatic), 3000-2800 (CH, saturated), 1801 (C=O, oxazolidinone), 1712 (C=O, carbamate), 1604, 1459, 1417, 1370, 1241, 1198, 1163, 1127, 1047, 1001, 753, 696. δ_H 9.31, 8.89 and 8.33-8.31, 2 x brs and m, 2H, NCHO and NCHC; 7.58-7.04, m, 9H, ArH; 5.21, brs, 3H, ArCH2 and NC**H**HO; 4.59-4.46, m, 2H, NCH**H**O and NCHCO; 3.57-3.22, m, 2H, NCHC**H**$_2$. δ_C 171.73, C=O; 159.13 NCHO; 155.53, OCON; 152.36, 135.25, 134.07 and 130.74, quaternary ArC; 128.65, 125.40, 124.67, 124.27, 120.91, 119.68, 118.70, 116.69, 115.91 and 109.49, ArC; 77.81, NCH_2O; 67.86, $ArCH_2$; 55.64, N**C**HCO; 26.11 and 25.06, NCH**C**H$_2$.

Example 6 Tryptophan

Attempted oxazolidination of the carbamate of tryptophan results in decomposition. This is presumably due to side reactions of the indole nitrogen. An electron withdrawing protecting group was anticipated to solve this problem and accordingly, the *N*-formyl tryptophan (70)[51] (Scheme 20) was prepared in quantitative yield from L-tryptophan (69). Carbamoylation then gave the precursor (71) for oxazolidination. The oxazolidination proceeded

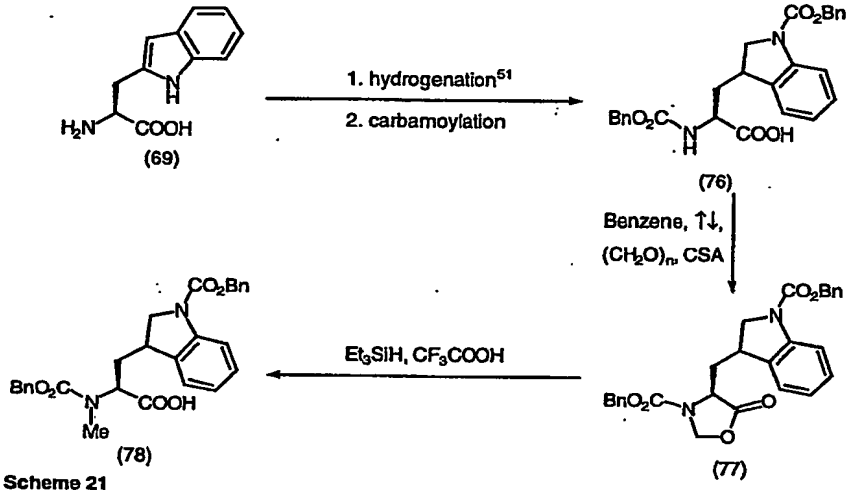
in good yield (86%) and the oxazolidinone (72) was isolated as an oil. The following reductive cleavage did not proceed as planned. In all cases two products were isolated. The minor product was the expected *N*-methyl tryptophan (73). The major product was the β-carboline (74). The β-carboline arises by reaction of the intermediate iminium ion with the indole in an intramolecular electrophilic aromatic substitution. The resulting carboxylic acid (74) was isolated as its *tert*-butylammonium salt (75).



Scheme 20

To further substantiate the role of the indole in the intramolecular interception of the iminium intermediate that leads to both the *N*-methyl tryptophan (73) and the β-carboline (74), the electrophilic aromatic substitution can be suppressed by reducing the pyrrole ring double bond. Accordingly, tryptophan (69) was converted to dihydrotryptophan (Scheme 21).[52] This material underwent bis-carbamoylation to give the precursor (76). Oxazolidination proceeded smoothly to afford the mixture of diastereoisomers (77). The key reductive cleavage proceeded as expected to afford the *N*-

methyl dihydrotryptophan (78) in 83% yield. This last result compares favourably with the tryptophan sequence (Scheme 20) which provided the *N*-methyl tryptophan (73) in only 22% yield and confirms the interference by the indole ring during the reductive cleavage.



Scheme 21

(S)-N-Carbonylbenzyloxy-N-methyl-N'-formyl-L-tryptophan (73) and (S)-2-Carbonylbenzyloxy-9-formyl-1,3,4,9-tetrahydro-β-carboline-3-carboxylic acid (74)

To a mixture of the oxazolidinone (72) (500 mg, 1.3 mmol), chloroform (8 ml) and triethylsilane (0.6 ml) was added trifluoroacetic acid (8 ml) and the whole was left to stand at room temperature for 2 d. The mixture was then concentrated at reduced pressure and the residue was taken up in ether. The ethereal solution was extracted with saturated aqueous sodium bicarbonate solution (3 x 10 ml). The combined aqueous extracts were acidified with dilute hydrochloric acid and extracted with dichloromethane (3 x 20 ml). The extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by column chromatography eluting with 95:5:0.5:0.2 chloroform:methanol:water:acetic acid to give firstly, the β-carboline (74) as an oil (340 mg, 69%). The β-carboline can be converted to the *tert*-butylammonium salt (75) by taking it up in ether and adding an equivalent of *tert*-butylamine. The precipitated *tert*-

butylammonium salt (75) can be recrystallised from hot methanol m.p. 162-165° (Found: C, 66.67; H, 6.54; N, 9.20. $C_{25}H_{29}N_3O_5$ requires C, 66.50; H, 6.47; N, 9.31%). $[\alpha]_D^{24}$ +41.3° (*c*, 1.0 in MeOH). ν_{max}/cm^{-1} (KBr disk) 3000-2800 (CH, saturated), 2743, 2636 and 2554 (NH_3^+), 1711 (C=O, carbamate), 1637 (CO_2^-), 1568, 1422, 1386, 1358, 1301, 1222, 1102, 1066, 748, 697. δ_H [(D$_6$)dimethylsulfoxide] 9.68, 9.32 and 8.21-7.93, 2 x brs and m, 4H, NCHO and NH_3^+; 7.48-7.23, m, 9H, ArH; 5.17-4.71, m, 5H, $ArCH_2$ and NCH_2C and NCHCO; 3.44-3.39, m, 1H, NCHC**H**H; 2.78-2.72, m, 1H, NCHCH**H**; 1.06, s, 9H, tBu. δ_C (rotamers) 172.56, CO_2^-; 159.08 NCHO; 155.94 and 155.77, OCON; 152.97, 137.14, 136.06, 135.27 and 130.34, quaternary ArC; 128.33, 127.70, 127.62, 127.42, 127.18, 123.75, 118.41, 114.77 and 110.76, ArC; 66.07, $ArCH_2$; 54.19, N**C**HCO; 50.06, **C**$(CH_3)_3$; 42.12, NCH_2C; 27.19 C(**C**$H_3)_3$; 23.44 and 23.21, NCH**C**H_2. Further elution afforded the *N*-methyl tryptophan (73) as a solid (110 mg, 22%) m.p. 129-130° (Found: C, 66.20; H, 5.39; N, 7.16. $C_{21}H_{20}N_2O_5$ requires C, 66.31; H, 5.30; N, 7.36%). $[\alpha]_D^{25}$ - 49.6° (*c*, 0.5 in $CHCl_3$). ν_{max}/cm^{-1} (KBr disk) 3600-3200 (CO_2H), 3091 and 3056 (CH, aromatic), 3000-2800 (CH, saturated), 1749 (C=O, acid), 1675 (CO, carbamate), 1605, 1459, 1392, 1319, 1251, 1191, 1135, 983, 795, 755, 699. δ_H (rotamers) 9.35, 8.83 and 8.38-8.36, 2 x brs and m, 2H, NCHO and NCHC; 7.63-6.94, m, 9H, ArH; 5.14-5.01, m, 3H, $ArCH_2$ and NCHCO; 3.50-3.09, m, 2H, NCHC**H**$_2$; 2.89-2.83, m, 3H, NCH_3. δ_C (rotamers) 175.25, CO_2H; 159.41, NCHO; 156.88, OCON; 155.94, 136.29, 135.92, 134.33 and 130.96, quaternary ArC; 128.52, 128.19, 127.79, 125.55, 124.89, 124.67, 124.21, 122.75, 119.75, 118.58, 116.26 and 109.71, ArC; 67.83 and 67.71, $ArCH_2$; 58.66 and 58.39, N**C**HCO; 31.97 and 31.81, NCH_3; 24.68 and 24.16, NCH**C**H_2.

(S)-3-Carbonylbenzyloxy-4-[1-carbonylbenzyloxy-2,3-dihydroindol-3(R,S)-ylmethyl]-oxazolidin-5-one (77)

The dihydrotryptophan (76)[29] (2.0 g, 4.2 mmol) was dissolved in toluene (100 ml) and the solution was

treated with camphorsulfonic acid (60 mg) and paraformaldehyde (5 g) and heated at reflux for 1 h. The clear solution was concentrated *in vacuo* and the residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), filtered and evaporated at reduced pressure to give a tan coloured oil (1.56 g). The oil was purified by column chromatography eluting with 20% ethyl acetate-hexane to give the oxazolidinone (77) as a colourless oil (1.38 g, 68%) (Found: C, 69.37; H, 5.67; N, 5.57. $C_{28}H_{26}N_2O_6$ requires C, 69.12; H, 5.39; N, 5.76%). ν_{max}/cm^{-1} (NaCl) 3000-2800 (CH, saturated), 1798 (C=O, oxazolidinone), 1712 (CO, carbamate), 1599, 1457, 1412, 1347, 1261, 1140, 1032, 752. δ_H 7.89-6.93, m, 14H, ArH; 5.53, brs, 1H, NCH**H**O; 5.26-5.09, m, 5H, 2 x $ArCH_2$ and NCH**H**O; 4.22-4.18 and 3.78-3.35, 2 x m, 4H, NCH_2CH and NCHCO; 2.31-2.12, m, 2H, NCHC**H**$_2$CH$_2$. δ_C 171.71, CO; 153.18 and 152.78, 2 x OCON; 142.01, 136.16, 135.01 and 132.87, quaternary ArC; 128.65, 128.49, 128.32, 128.12, 127.98, 123.86, 122.70 and 114.84, ArC; 77.63, 68.21 and 68.11, 2 x $ArCH_2$; 66.92, N**C**H$_2$CH; 53.56 and 53.16, N**C**HCO; 36.76 and 36.03, NCH**C**H$_2$; 35.66, NCH$_2$**C**H.

N,N'-bis-Carbonylbenzyloxy-3(R,S)-3-[2(S)-2-carboxy-2-methylamino-ethyl]-N-methyl-2,3-dihydroindole (78)

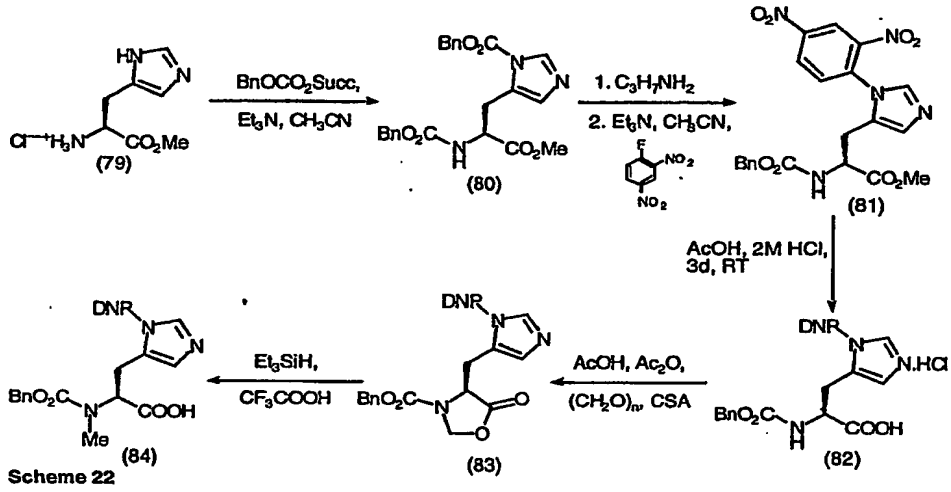
To a solution of the dihydrotryptophan oxazolidinone (77) (1.2 g, 2.5 mmol) in chloroform (13 ml) was added triethylsilane (1.2 ml) and trifluoroacetic acid (13 ml). The mixture was left to stand for 2 d and it was then diluted with toluene and concentrated under reduced pressure. The greenish residue was chromatographed on a short silica gel column eluting with chloroform-methanol-water 93:6.5:0.5. The appropriate fractions were collected and the solvent was removed *in vacuo*. The residue was further purified by chromatography eluting with the same solvent system to give the *N*-methyl dihydrotryptophan (78) as a clear pale yellow oil (1.0 g,

83%) (Found: M^+, 488.1944. $C_{28}H_{28}N_2O_6$ requires M^+, 488.1947). ν_{max}/cm^{-1} (NaCl) 3500-3200 (CO_2H), 3064 and 3038 (CH, aromatic), 3000-2800 (CH, saturated), 1703 (C=O), 1600, 1487, 1456, 1411, 1321, 1214, 1146, 1089, 1035, 971, 911, 856, 746, 697. δ_H 7.70-6.94, m, 14H, ArH; 5.26-5.11, m, 4H, 2 x $ArCH_2$; 5.00-4.90 and 4.77-4.69, 2 x m, 1H, NCHCO; 4.18-3.96 and 3.79-3.22, 2 x m, 3H, NCH_2CH; 2.95-2.88, m, 3H, NCH_3; 2.42-1.95, m, 2H, $NCHCH_2$. δ_C 174.75 and 174.48, CO_2H; 157.03 and 156.21, 2 x OCON; 152.87, 141.84, 136.16, 135.87 and 133.36, quaternary ArC; 128.49, 128.43, 128.14, 128.03, 127.67, 124.38, 123.52, 122.78 and 114.96, ArC; 67.77, and 67.02, 2 x $ArCH_2$; 57.03 and 56.74, NCHCO; 53.21, NCH_2CH; 36.28 NCH_2CH; 34.54 and 34.06, $NCHCH_2$; 31.07, NCH_3.

Example 7 Histidine

Again the basic and highly nucleophilic nature of the histidine sidechain caused problems in the initial attempts to form *N*-methyl histidine. Selective formation of the α-amino carbamate is difficult too. So the following sequence (Scheme 22) was adopted. Histidine methyl ester hydrochloride salt (79) was carbamoylated with two equivalents of (benzyloxycarbonyloxy)succinimide to give the bis-carbamate (80). Treatment of the bis-carbamate with propylamine effects removal of the imidazole carbamate. The reaction mixture was then evaporated under reduced pressure and the residue in acetonitrile was treated with 2,4-dinitrofluorobenzene, which undergoes a nucleophilic aromatic substitution to afford the dinitrophenyl imidazole (81). Treatment of this compound with a mixture of acetic acid and 2M hydrochloric acid resulted in hydrolysis of the methyl ester to afford the acid (82). The acid (82) is the precursor for the formation of the oxazolidinone. However, standard conditions for its formation could not be used due to the insolubility of the dinitrophenyl

derivative (82). This was overcome by dissolving the hydrochloride (82) in acetic acid and acetic anhydride in the presence of camphorsulfonic acid catalyst. Treatment of this mixture with paraformaldehyde afforded the required oxazolidinone (83) in high yield (>75%). Reductive cleavage then gave the *N*-methyl histidine carbamate (84) with the sidechain imidazole still protected with the dinitrophenyl group.



Scheme 22

N,N^{imid}-*Biscarbonylbenzyloxy-L-histidine methyl ester(80)*

A sample of the methyl ester (79) (1.0 g, 4.1 mmol) in acetonitrile (25 ml) was cooled to 0° with vigorous stirring and triethylamine (2.3 ml) was added followed by Z-Osucc (x) (2.16 g, 8.7 mmol). The reaction mixture was stirred at 0° for 30 min and then at room temperature overnight. The solution was concentrated at reduced pressure and the residue was taken up in ethyl acetate and washed with water (3 x 25 ml). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a pale yellow oil (1.57 g). The oil was purified by column chromatography on silica eluting with 40% ethyl acetate-hexane to give the carbamate (80) as a colourless oil which slowly crystallised on standing (1.3 g, 72%) m.p. 63-65 °C; $[\alpha]_D^{22}$ +28.0° (*c*, 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (KBr disk) 3175, 3139, 3108 and 3040 (CH, aromatic), 3000-2800 (CH, saturated), 1755 (C=O, ester), 1695 (C=O, carbamate),

1531, 1447, 1409, 1257, 1015, 871, 736, 697. δ_H 8.01, s, 1H, H2' or H5'; 7.41-7.24, m, 10H, ArH; 7.17, s, 1H, H5' or H2'; 6.10, d, *J* 8.1 Hz, 1H, NH; 5.35, s, 2H, $ArCH_2$; 5.07, s, 2H, ArCH2; 4.67-4.61, m, 1H, NCHCO; 3.68, s, 3H, OCH_3; 3.12-2.99, m, 2H, $CHCH_2$. δ_C 171.68, CO; 155.83, OCON; 148.13, 138.76, 136.25 and 133.78, quaternary ArC; 136.82, C5' or C2'; 129.04, 128.71, 128.58, 128.29 and 127.89, ArC; 114.51, C2' or C5'; 69.74 and 66.71, 2 x $ArCH_2$; 53.36, NCHCO; 52.25, OCH_3; 29.80, $CHCH_2$.

N-Carbonylbenzyloxy-N^{imid}-(2,4-dinitrophenyl)-L-histidine methyl ester (81)

The bis-carbamate (80) (1.0 g, 2.3 mmol) was dissolved in propylamine (30 ml) and the solution was left to stir at room temperature for 1 h. The solvent was removed by evaporation at reduced pressure. The residue was taken up in ethyl acetate (100 ml) and the solution was again concentrated under reduced pressure. The residue was taken up in acetonitrile (20 ml) and triethylamine (0.64 ml) was added in one portion followed by 1-fluoro-2,4-dinitrobenzene (336 µl) and the solution was left to stir in the dark overnight. The solution was concentrated *in vacuo* and the residue was taken up in ethyl acetate and washed with water (3 x 50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated to provide a crude yellow oil (1.5 g). The oil was chromatographed on silica eluting with 88:10:2 dichloromethane-acetone-methanol to give the methyl ester (81) as a yellow gum (0.9 g, 84%). $[\alpha]_D^{23}$ +23.7° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3109, 3067 and 3021 (CH, aromatic), 3000-2800 (CH, saturated), 1717 (C=O), 1609, 1536 and 1346 (NO_2), 1449, 1255, 1214, 1055, 911, 835, 743. δ_H 8.80, d, *J* 2.4 Hz, 1H, H-3"; 8.53, dd, *J* 2.4 and 8.7 Hz, 1H, H-5"; 7.76, s, 1H, H-2' or H-5'; 7.67, d, *J* 8.7 Hz, 1H, H-6"; 7.31-7.24, m, 5H, ArH; 6.84, s, 1H, H-5' or H-2'; 6.12, d, *J* 8.1 Hz, 1H, NH; 5.07, s, 2H, $ArCH_2$; 4.69-4.66, m, 1H, NCHCO; 3.17, s, 3H, OCH_3; 3.15, d, *J* 3.4 Hz,

2H, $CHCH_2$. δ_C 171.71, C=O ester; 155.97, OCON; 146.98, 144.32, 139.15 and 134.68, quaternary ArC; 136.46, C5′ or C2′; 129.35, 128.43, 128.30, 128.05 and 121.28, ArC; 117.44, C2′ or C5′; 66.89, $ArCH_2$; 53.48, NCHCO; 52.54, OCH_3; 29.85, $CHCH_2$.

N-Carbonylbenzyloxy-N^{imid}-(2,4-dinitrophenyl)-L-histidine hydrochloride salt(82)[61]

The methyl ester (81) (900 mg, 1.9 mmol) was dissolved in a mixture of glacial acetic acid (10 ml) and 2 M hydrochloric acid (10 ml) and the solution was left in the dark at room temperature for 3 d. The mixture was then concentrated at reduced pressure. The residue crystallised on standing and was purified by recrystallisation from methanol-ether to afford the hydrochloride salt (82) as a pale yellow solid (870 mg, 92%) m.p. 169-171° (Found: C, 48.87; H, 3.83; N, 14.23. $C_{20}H_{18}ClN_5O_8$ requires C, 48.84; H, 3.69; N, 14.24%). $[\alpha]_D^{30}$ -8.1° (*c*, 1.0 in MeOH). ν_{max}/cm^{-1} (KBr disk) 3200-2500, (CO_2H), 3112 and 3064 (CH, aromatic), 3000-2800 (CH, saturated), 2604, ($^+NH\ Cl^-$), 1705 (C=O), 1614, 1542 and 1345 (NO_2), 1447, 1389, 1241, 1056, 911, 843, 745, 697, 633. δ_H [(D6)dimethylsulfoxide] 9.48, s, 1H, NHCl, 9.00, s, 1H, H-3″; 8.81, d, *J* 8.7 Hz, 1H, H-5″; 8.15, d, *J* 8.7 Hz, 1H, H-6′′; 7.81-7.78, m, 2H, H-5′ and H-2′; 7.38-7.27, m, 5H, ArH; 5.03, d, J_{AB} 12.5 Hz, 1H, ArCHH; 4.99, d, J_{AB} 12.6 Hz, 1H, ArCHH; 4.46-4.39, m, 1H, NCHCO; 3.28-3.05, m, 2H, $CHCH_2$. δ_C (D6)dimethylsulfoxide, 172.20, CO2H; 156.06, OCON; 148.11, 143.87, 136.83, 132.99 and 131.86, quaternary ArC; 136.75, C5′ or C2′; 131.52, 129.45, 128.34, 127.87, 127.69 and 121.53, ArC; 120.56, C2′ or C5′; 65.61, $ArCH_2$; 52.90, NCHCO; 26.51, $CHCH_2$.

(S)-3-Carbonylbenzyloxy-4-[3H-3-(2,4-dinitrophenyl)-imidazol-4-ylmethyl]-oxazolidin-5-one (83)

To a solution of the carbamate (82) (200 mg, 0.4 mmol) in glacial acetic acid (5 ml) was added camphorsulfonic acid (10 mg), acetic anhydride (50 µl) and paraformaldehyde (50 mg). The mixture was heated with stirring at 85 °C for 2.5 h under a nitrogen atmosphere. The mixture was cooled to room temperature and then concentrated at reduced pressure. The residue was taken up in ethyl acetate and washed with aqueous sodium carbonate solution (10% w/v, 3 x 20 ml). The ethyl acetate phase was dried ($MgSO_4$), filtered and evaporated to dryness. The residual material was further purified by column chromatography eluting with ethyl acetate to give the oxazolidinone (83) as a yellow foam (133 mg, 66%) (Found: C, 53.82; H, 3.72. $C_{21}H_{17}N_5O_8$ requires C, 53.96; H, 3.67%). $[\alpha]_D^{25}$ +148.3° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr disk) 3110 (CH, aromatic), 3000-2800 (CH, saturated), 1800 (C=O, oxazolidinone), 1714 (C=O, carbamate), 1611, 1540 and 1352 (NO2), 1503, 1419, 1253, 1132, 1051, 748, 699. δ_H 8.81. d, *J* 2.5 Hz, 1H, H-3″; 8.54, dd, *J* 2.5 and 8.7 Hz, 1H, H-5″; 7.66, d, *J* 8.7 Hz, 1H, H-6″; 7.62, s, 1H, H-2′ or H-5′; 7.32-7.24, m, 5H, ArH; 6.84-6.64, m, 1H, H-5′ or H-2′; 5.37, brs, 1H, NC**H**HO; 5.26-5.10 m, 2H, $ArCH_2$; 4.89, d, *J* 3.7 Hz, 1H, NCH**H**O; 4.51-4.49, m, 1H, NCHCO; 3.49-3.37, m, 1H, CHC**H**H; 3.18, dd, *J* 2.4 and 14.9 Hz, 1H, CHCH**H**. δ_C 172.03, C=O oxazolidinone; 152.31, OCON; 146.95, 144.35, 138.27, 135.64 and 134.88, quaternary ArC; 136.69, C5′ or C2′; 129.36, 128.53, 128.39, 128.29 and 121.24, ArC; 117.95, C2′ or C5′; 78.10, NCH_2O; 67.69, $ArCH_2$; 54.61, NCHCO; 28.57 and 27.77, $CHCH_2$.

(S)-N-Carbonylbenzyloxy-N-methyl-N′-(2,4-dinitrophenyl)-L-histidine (84)

To a solution of the oxazolidinone (83) (460 mg, 1.0 mmol) in chloroform (5 ml) was added triethylsilane (470 µl) and trifluoroacetic acid (5 ml) and the reaction

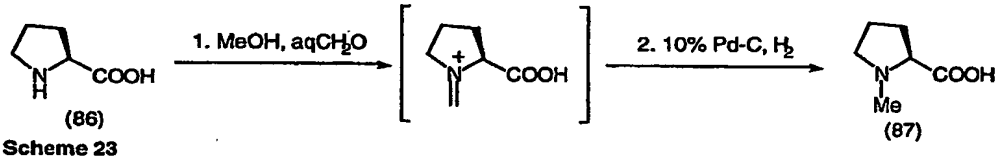
mixture was left to stand for 2 d. The solution was then concentrated under reduced pressure. The residue was taken up in a minimum of 95% chloroform-methanol and the precipitate, which formed, was filtered off at the pump to give the *N*-methyl amino acid (84) (225 mg). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography eluting with 92:7.5:0.5 chloroform-methanol-water to afford the *N*-methyl amino acid (84) (150 mg). The combined solids were recrystallised from methanol-ether to give the title compound (84) as a solid (375 mg, 81%) m.p. 165-167° (Found: C, 53.55; H, 4.07; N, 14.65. $C_{21}H_{19}N_5O_8$ requires C, 53.73; H, 4.08; N, 14.92%). $[\alpha]_D^{25}$ -24.7° (*c*, 1.0 in MeOH). ν_{max}/cm^{-1} (KBr disk) 3600-3200 (CO_2H), 3185, 3130 and 3041 (CH, aromatic), 3000-2800 (CH, saturated), 1734 (C=O, acid), 1680 (C=O, carbamate), 1618, 1545 and 1347 (CNO_2), 1492, 1460, 1402, 1308, 1187, 1143, 1087, 842. δ_H [(D_6)dimethyl sulfoxide] (rotamers) 8.92-8.91, m, 1H, H-3″; 8.65-8.62, m, 1H, H-5″; 7.98, brs, 1H, H-2′ or H-5′; 7.92-7.88, m, 1H, H-6″; 7.28-7.19, m, 6H, ArH and H-5′ or H-2′; 5.04-4.95, m, 2H, $ArCH_2$; 4.88-4.79, m, 1H, NCHCO; 3.13-2.99, m, 2H, $CHCH_2$; 2.82-2.79, m, 3H, NCH_3. δ_C (rotamers) 172.14, COOH; 155.80 and 155.47, OCON; 146.22, 143.52, 139.72, 136.85 and 134.63, quaternary ArC; 137.03, C2′ or C5′; 129.36, 128.69, 128.32, 127.67, 127.21, 127.11 and 121.32, ArC; 117.06 and 116.94, C5′ or C2′; 66.29 and 66.18, $ArCH_2$; 58.93 and 58.79, NCHCO; 31.83 and 31.64, NCH_3; 27.61 and 27.14, $CHCH_2$.

Example 8 Proline

Due to the tertiary substitution of the α-amino nitrogen in *N*-methyl proline there was limited interest on our part in its synthesis as it can not be readily incorporated in peptide sequences except at the *N*-terminus. The formation of the proline oxazolidinone (88) has been reported[53] though its synthesis is not high

yielding. The isolation of the oxazolidinone (85) can be avoided by the simple expedient of combining aqueous formaldehyde and proline (86) in methanol (Scheme 23). This mixture was then subjected to hydrogenating conditions to afford the *N*-methyl proline (87) in near quantitative yield. This approach was employed by Lin *et al.*[54] to prepare an *N*-methyl proline ester from a proline ester.

(85)



(86) (87)

Scheme 23

N-methyl-L-proline (87)

L-Proline (86) (2.0 g, 17.4 mmol) was dissolved in methanol (20 ml) and to this solution was added 40% aqueous formaldehyde solution (1.4 ml, 19.1 mmol). This was followed by the addition of 10% palladium-on-charcoal catalyst (500 mg) and the resulting slurry was stirred in a hydrogen atmosphere overnight. The slurry was then filtered through a celite pad to remove the catalyst. The pad was washed with methanol and the combined filtrates were concentrated under reduced pressure. The residue was taken up in ethanol-benzene (1:1, 100ml) and concentrated a second time to provide a solid, which was recrystallised from methanol-diethyl ether. In this way *N*-methyl proline (87) was isolated as fine needles (2.2 g, 98%) m.p. 142-145° (Found: M^+, 129.0784. Calc. for $C_6H_{11}NO_2$: M^+, 129.0790). $[\alpha]_D^{23}$ -78.0° (*c*, 2.0 in MeOH). ν_{max}/cm^{-1} (KBr disk) 3000-2800 (CH, saturated), 2675 and 2605 (ammonium ion), 1669 (CO_2H), 1612 (CO_2^-), 1468, 1401, 1354, 1327, 1234, 1183, 1112, 1056, 1025, 808, 775. δ_H (D_2O) 3.71-3.65

and 3.55-3.51, 2m, 1H, NCH_2; 3.00-2.91, m, 1H, NCHCO; 2.74, s, 3H, NCH3; 2.34-2.28, m, 1H, CHH; 1.99-1.78, m, 3H, CH_2 and CHH. δ_C 173.06, COOH; 70.18, NCHCO; 55.83, NCH_2; 40.26, NCH_3; 28.34 and 22.37, 2 × CH_2.

Summary of Examples

As the 5-oxazolidinone chemistry has been applied to the 20 common α-amino acids (and some others) in the formation of *N*-methyl derivatives, it is possible to classify the compounds according to their ease of manipulation. In the first group are those α-amino acids with sidechains that do not interfere with the oxazolidination and subsequent reductive cleavage. Into this group fits glycine, alanine, valine, leucine, isoleucine, phenylalanine, aspartic acid, glutamic acid, proline, tyrosine and phenylglycine. Historically, it is these amino acids that have been concentrated on by other workers.[53] Methionine gives one of the highest yields of the corresponding 5-oxazolidinone but does not react well in the reductive cleavage. The second category includes those α-amino acids for which a simple sidechain protection reaction that is also compatible with standard solid phase deprotection conditions allows their participation in the oxazolidinone chemistry. These amino acids are serine, threonine, cysteine, tyrosine, lysine, asparagine, glutamine and ornithine. Tyrosine has been included in both categories because while the *N*-methylation sequence works in moderate to low yield without the phenolic hydroxyl protected, sidechain benzylation substantially improves the yield. The third category is those amino acids that require devoted synthetic schemes and more exotic functional group protection. This group currently consists of the problematic α-amino acids arginine, homoarginine, histidine, tryptophan and methionine. These amino acids have collectively formed the substance of this paper. Currently, cystine constitutes a fourth category for which

this chemistry is not applicable, in whole or in part.

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It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Dated this 11th day of July 2002.
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By their Patent Attorneys
GRIFFITH HACK
Fellows Institute of Patent and
Trade Mark Attorneys of Australia